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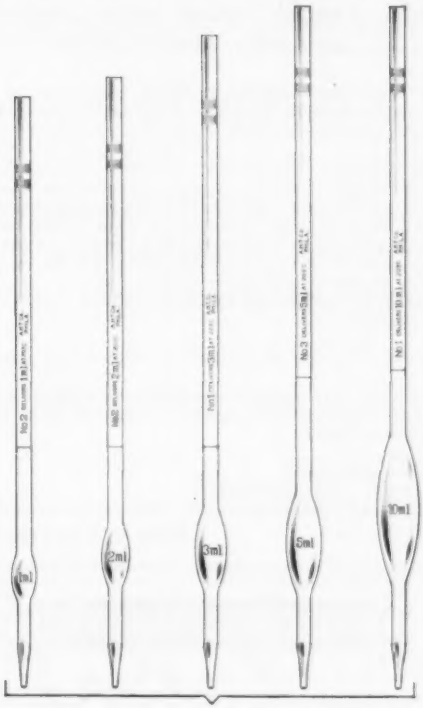

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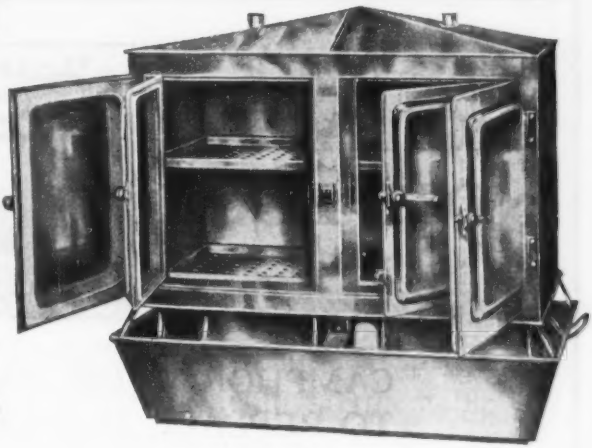

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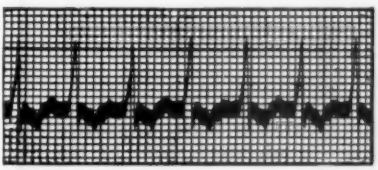

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Drs. Harlow Brooks and John Carroll in a paper on "The Management of the Heart in Pneumonia," say:

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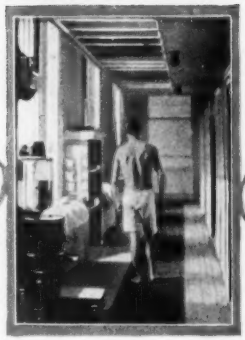

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JULY, 1924

ORIGINAL ARTICLES.

THE SURGERY OF PULMONARY TUBERCULOSIS.*

By John Alexander, M.A., B.S., M.D.,

ANN ARBOR, MICHIGAN.

I. Introduction.
II. The Evolution of Surgical Therapy.
III. Pathological Anatomy and Physiology.
IV. Thoracoplasty Compared With Artificial Pneumothorax.
V. Indications and Contraindications.
VI. Choice of Operation.
VII. Preoperative Management.
VIII. Anesthesia.
IX. Sauerbruch's Extrapleural Paravertebral Thoracoplasty.
X. Brauer's Subscapular Extrapleural Paravertebral Thoracoplasty.
XI. Extrapleural Pneumolysis.
XII. Open Intrapleural Pneumolysis.
XIII. Closed Intrapleural Pneumolysis.
XIV. Paralysis of the Diaphragm
XV. Tuberculosis Cavity of the Lung.
XVI. Tuberculosis Empyema.
XVII. Postoperative Course, Complications and Management.
XVIII. Deformity.
XIX. Results.
XX. Conclusions.
XXI. Bibliography.

Synopsis. The length of this paper requires that it appear in several installments. I therefore present here the following observations, which will be developed in the text:

1. On account of pleural adhesions, many patients with pulmonary tuberculosis that is mainly unilateral do not obtain from artificial pneumothorax the full benefit of lung compression therapy.

2. Many among them are in sufficiently good general physical condition for surgery. The operation of choice is paravertebral thoracoplasty.

* From the Department of Surgery, University of Michigan.

3. Any tuberculous lesions in the better lung should be inactive or only slowly progressive, if surgery is to be undertaken.

4. Cauterization, under thoracoscopic vision, of adhesions that are preventing adequate lung compression by pneumothorax should be reserved for those that are long, narrow and few in number.

5. In suitable cases operation should be performed as soon as artificial pneumothorax has proven itself ineffective; procrastination may rob these patients of an excellent chance of complete cure.

6. Thoracoplasty should be done in two stages, from two to three weeks apart. No fewer than 125 cm. of ribs XI to I inclusive should be resected.

7. Local and regional anesthesia is indicated for patients whose daily expectoration is more than 40 cc. When less than 40 cc, a combination of nitrous-oxide-oxygen narcosis and local and regional anesthesia is best.

8. The immediate and remote dangers of any operation that compresses only a part of a hemithorax are greater than its advantages, except in unusual cases. This does not apply to a combination of partial thoracoplasty and partial artificial pneumothorax.

9. Neurexairesis of the phrenic nerve may be performed with advantage before every thoracoplasty and after every artificial pneumothorax.

10. Some stiff-walled apical cavities are not obliterated by paravertebral thoracoplasty. The supplementary operation of parasternal thoracoplasty, or of pneumolysis with muscle, fat, gauze or paraffine "fill" should be considered, but not performed sooner than six months after the primary operation.

11. Some cavities cannot be collapsed, and by retention of secretions cause severe toxemia. Drainage is occasionally indicated for them.

12. Tuberculous empyema is best treated by repeated aspirations and air replacements, and sometimes with antiseptic instillations or irrigations. Only in the presence of dangerous secondary infection may open or close tube drainage be used. Persistent empyemas, especially if complicated by fistula, often require thoracoplasty for their cure.

13. Favorable results in the surgery of pulmonary tuberculosis depend upon great discretion in the selection of cases, early and skilfully executed complete operations and strict attention to postoperative care, including not less than six months "curing," preferably at a sanitorium.

14. Among 1024 cases of advanced tuberculosis, reported from 1918 to 1923, there was a mortality of 12 per cent during the first month after operation (the immediate operative mortality was about 2 per cent), and 19 per cent thereafter, mostly from tuberculosis in the originally better lung or other organs. Twenty-six per cent were improved, and 32 per cent were cured. Of the 824 patients

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managed according to the criteria given in paragraph 13, immediately above, 26 per cent were improved, and 33 per cent cured.

I. Introduction. A therapy for certain selected cases of desperate advanced pulmonary tuberculosis that cures 33 per cent of the patients, and improves an additional 26 per cent, deserves and demands more rapid adoption in the United States than it is now receiving. It may be conservatively estimated that at present there are in this country 15,000 persons with pulmonary tuberculosis for whom surgical interference is indicated, many of whom are living at home, too diseased for admission to sanitoria, spreading infection and unable to work, and, if unaided, almost certainly doomed to die.

Except when especially indicated to the contrary, the various divisions of this paper concern themselves with the operation of paravertebral extrapleural thoracoplasty (resection of the posterior ends of the ribs), upon which, as a foundation, modern surgery of pulmonary tuberculosis is built.

Within the past five years Sauerbruch of Zurich and Munich has alone reported over 500 operated cases, while the total number from all clinics in the United States and Canada is 110. Archibald of Montreal was the first to operate in America (1912), and has since performed 40 additional operations. Shivers of Colorado Springs has operated upon 27 patients since 1914, Lilienthal of New York 12, Law of Minneapolis 11, Welles of Saranac Lake 11, Eloesser of San Francisco 5, Willy Meyer of New York 5, and there have been other smaller series. During fifteen years and more, surgical compression therapy has been developed and extensively practised in Switzerland, Germany, Scandinavia and Denmark, and has earned for itself a sure and permanent place. North and South America, England, Spain, Italy, Belgium and France are only now commencing to be aware of its remarkable value, and to use it.

The reasons why these last named countries have delayed so long are easily understood. Chief among them is ignorance of the method, its indications, execution and results. This lack of familiarity is not suprising in view of the fact that it has always been a slow process for highly specialized procedures to overcome international language barriers. In view of the known facts, however, it is discouraging to find only three pages devoted to the method in the 1922 edition of a standard American text-book on tuberculosis, and only nine small pages in a 1920 volume of a 32 volume French system of medicine, and both of these accounts uninformed, inaccurate and misleading. Other recent books cite the technic and results of the Brauer-Friedrich and the Lenhartz operations of fifteen years ago as illustrative of modern technic and results, and completely ignore the revolutionary changes brought about by the two-stage.

paravertebral operation. On the other hand, it is somewhat encouraging to know that such an authority as Krause has recently written that the German results warrant more extensive use of surgery, and that he believes that the method will be accepted by the profession for certain advanced forms of the disease.

There exists today among many physicians and patients a hazy notion that the operative shock and mortality are terrific, the postoperative pain scarcely endurable, and that the survivors, grossly mutilated and crippled, may only hope to drag themselves through a few extra years of burdensome life, and, indeed, that permanent clinical success is a rarity. That this notion is not based upon fact is evident to anyone who is acquainted with present day technic and results.

A further not insignificant reason for the unduly slow popularization of surgical compression therapy is that certain monographs, purporting to represent and illustrate standard procedure, but actually describing inefficient, if not dangerous methods, appear from time to time, and are obliged to report such high mortalities and poor final results that those seeking information are driven away from surgery rather than informed and attracted. Indications and contraindications are often badly placed, and bizarre operative technic described. Probably the two greatest sins are: (1) the reporting of cases as operated upon by the "Sauerbruch technic" when the first rib has not been touched (except in rare cases resection of a portion of that rib is an essential step in the operation), and (2) the use of partial operations, half-measures, when the widest experience has demonstrated that only total operation may be expected to produce the successful result desired.

As no comprehensive survey of modern compression therapy exists in the English language, it is the purpose of this paper to outline a standard procedure that may be expected to give the best results in the light of modern knowledge, in the hope that it may help the profession to understand and to popularize it some years in advance of the time when it would "arrive" by the normal processes of diffusion. The paper is based upon a critical review and analysis of the world's literature of the past six years.

Artificial pneumothorax is now firmly established in this country, and where indicated is being used often and early, frequently with miraculous results. When, on account of pleural adhesions, satisfactory compression cannot be obtained with air, equal and sometimes better results are obtainable with surgery. Although there is now an increasing reluctance among physicians to condemn surgical compression in pulmonary tuberculosis "on general principles," as many did a few years ago, it is as yet rarely advised, largely I think, because it is so little understood outside of Central Europe. Skilful surgical management demands special knowledge and training, and until a greater number of well-grounded surgeons

have manifested their interest and properly equipped themselves, tuberculosis specialists and physicians in general will be very reluctant to recommend to their patients so specialized an operation. Once the surgeons have demonstrated their interest the internists will speedily avail themselves of the opportunity.

II. The Evolution of Surgical Therapy. The surgical therapy of pulmonary tuberculosis has followed many blind paths; it has been only during the past thirty-five years that the present type of operation has been in process of development.

Drainage of tuberculous cavities has been practised in isolated cases for many centuries, but rarely advocated with enthusiasm. In 1885, de Cerenville, however, published a small series of personal cases and believed that the method had a promising future. In recent years Sauerbruch has become a strong advocate of drainage in selected cases.

Many unsuccessful attempts have been made to influence the progress of tuberculous lesions by direct application of medicaments by the tracheal or intercostal routes. Baglivi in 1696 introduced them after intercostal incision. Mosler in 1875 injected phenol and other drugs through a needle directly into the areas of maximum pathology, as well as into cavities after aspiration of their contents. Koch used tincture of iodin. Gessner in 1904 reported not unfavorable results (cough and sputum somewhat reduced) from the injection of iodoform and glycerin, or zinc chloride, or alcohol. The drugs were intended to disinfect and to stimulate the growth of fibrous tissue. As they could reach only a very small number of the diffuse lesions these actions must be without notable, favorable results. The dangers of causing sloughs, and of injecting highly irritating drugs into bloodvessels or bronchi are considerable.

In 1858, Freund started a controversy that only now is dying. He claimed after extensive postmortem observations that active apical tuberculosis was more common in those whose first rib was shorter, or whose first cartilage was stiffer than normal, and that not infrequently he had seen healing in such cases where there had been spontaneous rupture of the cartilage and new joint formation. He believed that the stenosis of the upper thoracic aperture caused an insufficient blood supply, and stasis of lymph and bronchial secretions, and consequently lodgment and growth of any tubercle bacilli that might happen to be present. That apical tuberculosis only rarely occurs in children he explained on the ground that in them the apex is normally below the first rib, and therefore uninfluenced by its abnormalities. Concretely, he proposed to section, or partially to resect the first cartilage, thereby mobilizing the apex, and permitting it to share in full respiratory excursions. Freund's contentions were strongly supported by Hart and Harris and by many others. Bachmeister showed experimentally that artificial narrowing of the thoracic inlet determined the localization of tuber-

culosis. Many pathologists have noted the concentration of tubercles beneath the groove (Schmorl's) sometimes made in the lung by the first rib. Recently Kaiser, of Jessen's Clinic, has reported a study of 600 roentgenograms, from which he concludes that the localization and development of tubercles is definitely determined by the ossification, narrowness or anomalous position of the thoracic inlet. Valker in 1919 reported the combination of apical disease and stenosis in 54.29 per cent of 35 dissected cases, and presented a mathematical formula for determining the size of the inlet.

Kausch has performed the Freund operation 9 times, and 7 were improved or cured. At present those who accept the Freund theory are unanimous in condemning the operation as being too radical for very early lesions, and ineffective for developed ones, but do advocate the systematic use of breathing exercises as prophylaxis against tuberculosis where inlet stenosis exists. Sauerbruch suggests possibly using Freund's operation upon a healthy child, with inlet stenosis, who has been exposed to tuberculous infection, and whose chest is so inelastic as to be uninfluenced by breathing exercises.

At present a majority of clinicians deny the validity of the theory, claiming that the figures offered in support of it are far from convincing, and that the ossification of the first cartilage is frequently a sequel of the tuberculosis, rather than a primary determining factor. Hofbauer points out the danger of checking the further growth of the first rib of a child by operative interference with its epiphysis. Kausch, Blanc and Fortacin, and others have said with much reason that the removal of a small section of the first cartilage causes rest and a small compression of the apex, and not an increase in respiratory excursion, and that any favorable results that may have been observed were due to a true thoracoplasty, although a very small one.

It is not surprising that actual resection of diseased lung tissue should have been attempted, after successful experiments upon animals. Tuffier, Lawson, Doyen, W. Macewen and Sauerbruch have reported successful operations upon man; Block, Ruggi, von Herff, W. Müller and Réclus have also done it, but unsuccessfully, and usually with fatal results. In all there have been only 3 or 4 somewhat permanent cures, and 7 reported deaths. The objections to such an operation are outstanding: (1) Pulmonary tuberculosis is almost never strictly localized to one lobe, or to a part of a lobe, and there is almost always lymphatic extension to the hilus. Therefore conservative resections cannot extirpate all of the disease; (2) unless the resection were small enough to permit the vacant space to become filled by the shifting of neighboring organs, or by compensatory emphysema, a subsequent thoracoplasty would be necessary to obliterate it, thereby exposing the patient to the dangers of two major operations; (3) sanitarium treatment offers most excellent chances of cure for those localized, minimal lesions for which resec-

tion might be considered indicated, and is without risk. The only modern indication for resection is where one entire lung is almost completely destroyed by cavity formation, and the other lung is in fair condition; under differential pressure anesthesia, a wedge including the huge cavity should be removed. The successful cases of Macewen and of Sauerbruch, noted above, were of this type.

The favorable influence of pleural effusions and of spontaneous pneumothorax (if the patient survives the shock) upon largely unilateral pulmonary tuberculosis has been known for many years. Spaeth remarked it in 1850, and more recently von Muralt has reported the cure of 6 out of 33 patients in whom spontaneous pneumothorax had occurred. Such observations suggested to Forlanini in 1882 the use of artificial pneumothorax, and were also responsible for the independent development of pulmonary compression by rib resection. It is a curious fact that for more than twenty years it occurred to no one that the effect of artificial pneumothorax and of thoracoplasty upon tuberculous lungs was exactly the same—a mechanical relaxation or compression, and it was not until then (1907) that Brauer laid down the hard and fast rule, which holds inflexibly today, that primary thoracoplasty is never indicated when a satisfactory compression is obtainable with artificial pneumothorax.

One hundred years ago James Carson predicted that if a cure were to be found for pulmonary tuberculosis it would be by surgical operation, effecting a mechanical compression that would put the diseased parts in a quiescent state. In 1885 the first attempts in this direction were made by de Cerenville of Lausanne, thereby initiating the method that is used today. The operative technic of all his work and of the many subsequent modifications was based upon the operations which had already been performed by Simon (1869), de Cerenville (1877) and Estlander (1879) for chronic empyema. de Cerenville's 1885 report demonstrates that he understood the necessity of breaking the continuity of the bony, non-yielding thoracic cage, in order to effect collapse of pulmonary cavities. He operated in 4 cases of apical cavity, 2 of which he drained; although he resected only 3.5 cm. of the second and third ribs anteriorly, or "as many as necessary, according to the extent of the cavity," he observed definite pulling in of the sectioned ribs and consequent lessening of the size of the cavities. Independently, Quincke did the same thing in 1888, and in 1896 urged small rib resections for non-cavernous types of tuberculosis as well. Independently of him Carl Spengler in 1890 resected greater lengths of ribs from under the scapula via a periscapular incision in cases in which pleural effusions had occurred; he aspirated the effusions before operation. Spengler called his operation "extrapleural thoracoplasty," the name used today for the standard operation. Turban in 1899 also operated for non-cavernous types of tuberculosis, and

resected as many as 65 cm. of ribs IV to X. In 1901 and 1903 Garrè and Quincke first urged thoracoplasty for hemoptysis, and advocated supplementing it with an extrapleural pneumolysis. In 1902 Landerer resected from 4 to 8 cm. of ribs I to V anteriorly, or ribs II to VIII, or IV to IX posteriorly.

The results of all of the preceding procedures were unsatisfactory, and Brauer realized that clinical success depended upon obtaining a pulmonary compression comparable in amount with that obtained by artificial pneumothorax, which was already effecting remarkable cures. Therefore, instead of the limited resections practised hitherto he proposed the removal of the entire lengths of ribs II to X at one sitting, in order to obtain actual compression of lung, instead of mere relaxation. Friedrich, his surgeon, first operated by this method in December, 1907, and the result was highly satisfactory. However, in their series of 29 cases there were 8 operative deaths, a mortality of 27.5 per cent; there were 6 complete cures, 20.7 per cent. Lenhartz used the same technic, and in addition pressed the apex toward the hilus, and killed 19 of 20 patients. Sauerbruch has used the Brauer-Friedrich technic upon 71 patients, 62 of whom, however, he operated in two or more stages; his only operative deaths, 2 in number, occurred after single stage operations. His combined early and late deaths totaled 31 (43.6 per cent), his improvements 12 (16.9 per cent), and complete cures 28 (39.4 per cent).

It was soon realized that this operation was highly dangerous. The operative shock was terrific; the side of the chest operated upon, being deprived of all of its bony support, swung in and out freely with the respiratory movements, but in a paradoxical sense, and this swinging was shared by the mediastinum (unless it was firmly fixed by adhesions), and consequently the opposite lung was narrowed, respirations became rapid and superficial, the circulation not infrequently failed, and many patients soon died of acute respiratory insufficiency. Because of the labored respirations of the opposite lung, rapid progress of minimal lesions there was frequently observed.

At first Friedrich operated rapidly under light general narcosis, supplemented by local anesthesia. Through a Schede incision (horseshoe-shaped: down the front of the chest, across it laterally and up between the spine and scapula) he removed 10 to 25 cm. each of ribs II to X (together with their periosteum and intercostal muscles), a total of 130, 160 or 200 cm., leaving the first rib in order to save time, expecting it to become depressed as the chest gradually narrowed. Later he modified this technic by using regional and local anesthesia alone, operated more slowly, resected the first rib as he found he could not count upon its "settling" enough to give satisfactory apical compression, left the anterior ends of the ribs as he saw that they helped greatly to prevent chest flutter, and that

they bent in at the cartilages as pulmonary scar tissue contracted, and left the periosteum and intercostal muscles intact, as lung herniæ were common when they were removed. As thus modified, it will be seen that the Brauer-Friedrich operation was similar to an Estlander operation for chronic empyema.

At present the Brauer-Friedrich operation is obsolescent because of its many dangers. It is still sporadically used for rare cases where the pleura and mediastinum are known to be so thickened by adhesions that mediastinal displacement and flutter are not to be feared. Even then it would be used only by dividing it into two or more stages.

Brauer has modified this original operation of his, eliminating the major dangers and yet obtaining great compression and excellent clinical results. It will be described in a later instalment.

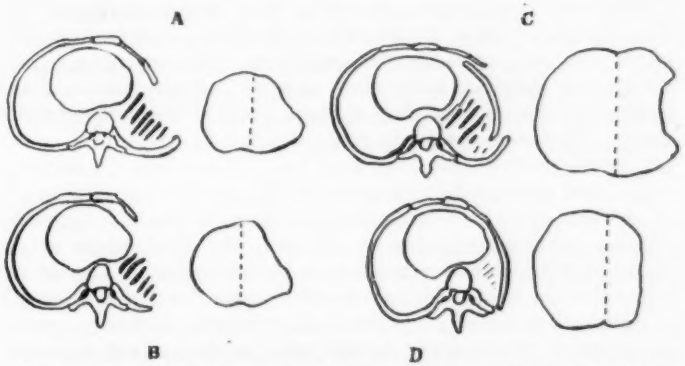

FIG. 1.—Diagrams illustrating the relative reduction in capacity of the hemithorax after various types of rib resection. *A*, Estlander technic: five ribs resected; chest circumference reduced 4 cm.; *B*, Gayet-Estlander: 110 cm. resected from eight ribs; circumference reduced 5.5 cm.; *C*, Quénu: small resections of seven ribs; circumference reduced 3 cm.; *D*, Boiffin-Gourdet: 54 cm. resected from nine ribs; circumference reduced 8 cm. It is this type of resection that is used in the modern operation for tuberculosis. (After Brauer and Spengler, from Boiffin and Gourdet).

In 1923 Davies proposed a modification of the Brauer-Friedrich operation that seems to have almost nothing to recommend it. He makes a long vertical incision in the midaxillary line and resects ribs II to IX from their costochondral junctions to about their angles. He states that the first rib needs removal only rarely, as the whole anterior and lateral chest sinks in; if it requires removal later, it could be done through a separate incision below the clavicle, he says. The disadvantages of this operation are that it exposes the patient to the dangers of the Brauer-Friedrich operation, and does not take advantage of the fact, well-known since the beautiful demonstrations of Boiffin and Gourdet, that removal of those parts

of the ribs posterior to their angles (over the costovertebral gutter) is essential for satisfactory compression; further, it is firmly established that in a huge majority of cases it is necessary to resect the first rib in order to compress the apex, which is apt to contain the most advanced disease. Bayer, C. Spengler and Sauerbruch have also removed lateral rib sections through an axillary incision, but abandoned this technic as the anterior and posterior rib stumps were seen to spring out instead of to fall in. This same springing-out has been noted when only the anterior ends of the ribs are removed, parasternally.

As the Brauer-Friedrich operation was a reaction against the restricted resections of the earlier thoracoplasties, so the present types of operation are compromises between the two—extensive enough for favorable clinical effect, and yet conservative enough to avoid unusual operative dangers.

Wilms realized that the removal of short lengths of ribs at their posterior ends, that is, from just in front of their angles all the way to the transverse processes of the vertebræ, would not only give relatively great reduction in the chest capacity, without chest-wall and mediastinal flutter, but that it could be done without operative shock. There was not an operative death in his series of 23 cases. At first he resected only from 2 to 4 cm. of ribs I to V paravertebrally, and at a second sitting two to four weeks later, 2 to 4 cm. of rib-cartilages I to V parasternally. This operation is known as "Wilms columnar resection." He soon saw that better results would be obtainable by extending his resections further beyond the limits of gross disease; he then resected as far down as the seventh or eighth rib posteriorly and the sixth or seventh anteriorly, operating in two or three stages. At this period he did not fear aspiration into the lower lobe of infected secretions which were pressed out of the upper lobes by thoracoplasty. By 1913 he was well aware of this danger, and removed, at the *first* sitting, from 10 to 20 cm. of ribs VII, VIII and IX, and lesser lengths of the mid-ribs; at a second sitting, 4 to 5 cm. of the upper ribs, including the first; at a third sitting, 2 to 3 cm. of ribs I to V parasternally, and possibly the inner end of the clavicle, in order to obtain the compressing weight of the shoulder against the lung. At the present time he never resects the clavicle, and only exceptionally adds the parasternal resections.

Sauerbruch, once Friedrich's assistant, should be given great credit for having urged and practised many of the improvements which are part of the final Wilms technic, and in fact this operation is now generally known by the name of "Sauerbruch's paravertebral extrapleural thoracoplasty." It was Sauerbruch who insisted upon doing the posterior operation in more than one stage, and in removing the lower ribs first to check the lower lobe's respiratory function in order to lessen the chances of aspiration when the more extensively diseased upper lobes were later compressed. It was he who urged

local and regional anesthesia, and proposed the convenient hook-shaped incision, embracing the angle of the scapula. With his tremendous experience of over 500 cases, his opinion in regard to the surgical therapy of pulmonary tuberculosis is generally accepted as law.

In recent years a number of rather bizarre operations have been proposed, but none of them have gained favor, or are likely to. In 1913 Alvarez operated upon 4 cases of advanced tuberculosis, stretching the second, third and fourth intercostal nerves in order to paralyze, by excess of stimulation via the rami communicantes, the vasoconstrictor fibers of the sympathetic nerves to the lung. He hoped to produce an active congestion of the lung and, so, favorably to influence the disease. He reported that mild to absolute dulness occurred for from three to six days after these operations, and that there was noted a temporary clinical improvement—better appetite, weight and sleep, less sputum and fever. The improvement was only temporary, and 3 of the 4 soon died. Codina has reported a case which was markedly improved, as shown by a loss of tubercle bacilli and a gain of 7 kg. in weight in two months. Friedrich and Warstat practised the operation and their results were poor. Alvarez now proposes resection of the second, third and fourth sympathetics within the chest (extrapleural approach), hoping to obtain a permanent congestion of the lung. This modification has never been used upon man, but Lapeyre has done it upon normal dogs. As at present developed, there is nothing better than poorly supported theory in favor of Alvarez's sympathetic operation.

Bruns and Sauerbruch have proposed ligation of lobe branches of the pulmonary artery, and Tiegel of the vein, in order to cause dense fibrosis of the lobe. Artery ligation has been used with some success for bronchiectasis in man, but the adhesions in most cases of advanced pulmonary tuberculosis would prevent ready access to the hilus. However, in 1923 Schlapfer advocated a combination of ligation of the pulmonary artery and phrenicotomy for tuberculosis in man; he would expect this to effect clinical healing, or prepare the lung for a relatively safe secondary lobectomy, which would eradicate remaining foci. He further proposed partially to occlude the pulmonary veins with Halstead bands, which would later be removed, as a "partially curative, partially preventative" measure against slight unilateral tuberculous infection in the presence of a strong tuberculous family history. Two important objections may be made to these propositions: (1) the rather extreme pulmonary fibrosis that would follow either operation would probably demand subsequent thoracoplasty to compensate for the traction displacements produced, in spite of the phrenicotomy; (2) any intrapleural operation, involving the separation of adhesions, upon an actively tuberculous person has proven gravely dangerous.

Artificial pneumothorax and thoracoplasty now offer such excellent chances of success that they will not give place to such dangerous and complicated procedures as these.

Experimentally Henschen has produced great pulmonary fibrosis by: (1) sewing the fascia lata tightly over one or more lobes, or (2) displacing the lower lobe beneath the diaphragm, through an incision in its fibers, or (3) severing the attachments of the diaphragm, thereby allowing it to rise (even as high as the second rib), and compress the lung.

Warstat has experimentally resected or stretched all the intercostal nerves on one side, and he observed a great flattening of that side—a "cadaveric position" with almost no respiratory movements, and marked fibrosis of the lung. Into some of his operated animals he injected tubercle bacilli intravenously, and at necropsy saw the usual active, large, caseous tubercles in the lung of the unoperated side of the chest, but only small, non-caseous tubercles on the compressed side. He then operated upon two men with cavity formation, one of whom had had a previous phrenicotomy; in both there was great flattening of the operated side, and no harm from the abdominal wall paralysis. Morales twisted out 12 intercostal nerves on one side in several cases, and obtained favorable results in a few. As the intercostal nerve operations are nearly as severe as Sauerbruch's thoracoplasty, and are less effective, and as there is some danger of tearing the pleura while searching for the nerves, it is not likely that these operations will ever become popular.

In 1917 Kronberger proposed and practised resection of sections of alternate ribs, or 2 out of every 3 ribs, on the theory that it would permit considerable lung retraction and at the same time preserve the function of that lung, and not threaten the circulation. As this major operation produces no compression or rest of the diseased parts, but only a small relaxation, it will never gain favor.

III. Pathological Anatomy and Physiology.* Sauerbruch cites the history of a patient upon whom he performed thoracoplasty on account of repeated hemorrhages and cavitation in one lung, in spite of active disease in the other lung; the patient died three months later. There was seen at necropsy a definite tendency to encapsulation, with young connective tissue, of all tubercles and caseous nodules in the compressed lung; its cavities were mere clefts, which were being filled with new granulation tissue containing many bloodvessels. The uncompressed lung showed new cavity formation and extensive caseous pneumonia, but *without any tendency whatsoever toward encapsulation*. That the far-advanced lesions in the compressed lung of a dying person were able to progress so far toward arrest in a period of three months is illustrative of the effect of compression. Jessen is correct in saying that the problem of advanced pulmonary tuberculosis is a mechanical one, as well as an immunological one.

* Also see DEFORMITY.

While bed-rest considerably quiets respiration, it is not able to put the lung at complete rest, nor to protect it against the violent movements of coughing. Compression therapy not only does this, and thereby largely checks the movement of toxin-laden lymph into the general circulation and of bacilli-laden lymph to new situations in the lungs, but empties the lungs of accumulated products of degeneration, and, by flattening the lumina of the bronchi and alveoli, prevents the spread of infection by the bronchial tree route; most important of all, it is directly responsible for a rapid new growth of fibrous tissue which encapsulates the lesions and eliminates the disease.

There is some difference of opinion as to how much thoracoplasty lessens the capacity of the chest; this depends considerably upon the lengths of ribs removed, and upon whether or not the sections

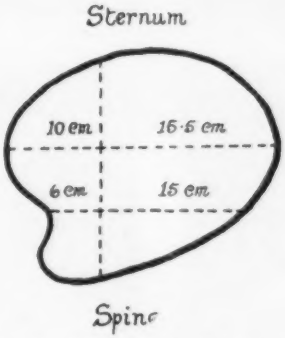

FIG. 2.—Cyrtometric diagram showing diminution in area of the left hemithorax following paravertebral thoracoplasty. (After Bérard and Dumarest.)

between the angles and heads of the ribs have been resected. Over thirty years ago Boiffin and Gourdet showed upon cadavers that if these portions were included in the resections, removal of a total of 54 cm. from 9 ribs reduced the chest circumference 8 cm., whereas if these portions were not removed and the resections were made anterior to the rib angles, a total of 110 cm. from 8 ribs would reduce the chest circumference only 5.5 cm. (see Fig. 1). Saugmann, who removed an average of 134 cm. from 10 ribs and included their posterior extremities, found at a necropsy a reduction of from $\frac{1}{3}$ to $\frac{1}{2}$ of the normal chest capacity. Sauerbruch says that after his operation the chest capacity is reduced only 300 to 500 cc; Brauer says that his radical thoracoplasty effects a reduction of 3000 cc, which corresponds to two-thirds the volume of a complete pneumothorax. Madinier considers the amounts of compression of the lung after a good thoracoplasty and a large partial pneumothorax approximately equal. The clinical results given under thoracoplasty compared with artificial pneumothorax show that thoracoplasty is

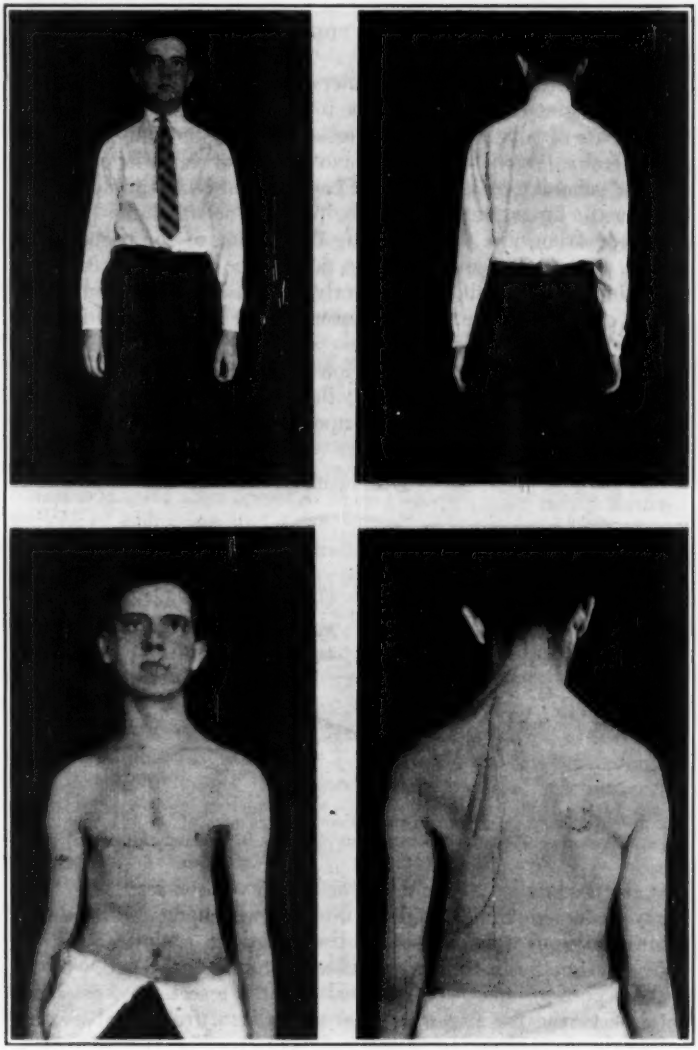

FIG. 3.*—A. H., one year after paravertebral thoracoplasty. Inconspicuous scar. The small amount of apparent gross deformity should be compared with the actual reduction in chest capacity as shown in Fig. 5.

Before operation this patient was in poor condition, confined to bed, weighed 114 pounds (normal, 126 pounds); temperature 99.6°, pulse 90; left lung, far advanced tuberculosis with cavity in upper lobe; right lung moderately advanced tuberculosis; 150 cc sputum daily; blood-streaked and positive for tubercle bacilli; had "cured" for two years. At the time these photographs were taken, one year after operation, he was in good condition, weighed 130 pounds; temperature normal, pulse 76; cavity obliterated, right lung inactive; 10 cc sputum daily and steadily decreasing, and tubercle bacilli absent; still under treatment at sanitarium. Further illustrations of this patient will be seen in Figs. 4, 5, 12, and 13.

* Figs. 3, 4, 5, 12, 13 and 14 have been courteously furnished by Dr. E. S. Welles, of Saranac Lake, N. Y.

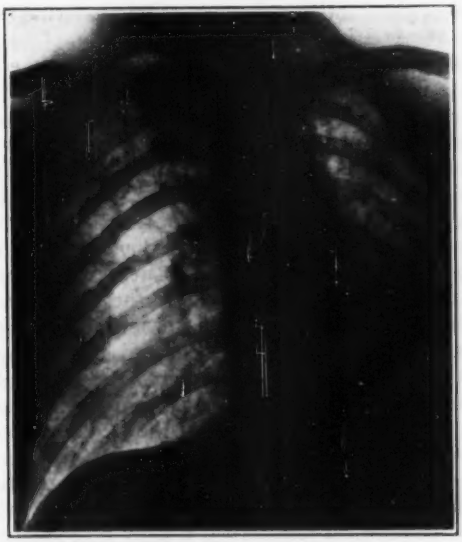

FIG. 4.—A. H., before operation. Far advanced tuberculosis of whole left lung: cavity upper lobe. Moderately advanced disease of right lung.

FIG. 5.—A. H., one year after operation. Cavity obliterated. Compare with Figs. 3, 4, 12 and 13.

not inferior to pneumothorax because of its producing less complete pulmonary compression.

As thoracoplasty removes the posterior ends of the ribs and as the gaps are usually filled with new bone without joint formation, the bony cage on the operated side is no longer able to share in respiratory movements, and as dense pleural adhesions soon follow the operation, the diaphragm becomes fixed and greatly restricted in function. On the other hand, the removal of great lengths of rib, as in the old Brauer-Friedrich operation, leaves a flaccid chest wall which may not become fixed by new bone formation and which swings inward with inspiration, and outward with expiration—a paradoxical movement which allows the stale air within the collapsed lung to be drawn into the uncompressed lung during inspiration, and blown back into the collapsed lung during expiration—so-called "pendulum respiration." Further, the effect of any movement, paradoxical or otherwise, upon the grossly diseased lung is in opposition to one of the chief aims of the treatment, namely rest. As the Sauerbruch operation removes only short lengths of rib, the heavy overlying muscles, and, later, new bone formation prevent unfavorable movements of the compressed lung. Although Hug found some paradoxical respiration, usually posterolaterally, in 21 out of 22 of Sauerbruch's and Schreiber's patients at Davos, it was never of marked degree.

Cloetta has clearly shown that a moderate pulmonary compression, such as occurs with the modern thoracoplasty or with a moderate pneumothorax, causes a greater, rather than a lesser blood supply to the lung, because when the lung is fully expanded in its normal position the bloodvessels are stretched and narrowed, but when the lung is relaxed the vessels are relaxed and broadened. Microscopically the vessels are seen to be dilated. However, if the pulmonary compression is great the bloodvessels are narrowed and the blood supply is definitely less, and this is contributed to by whatever shrunken fibrous tissue exists in the lung. So, whether a compressed lung is better or worse supplied with blood depends upon the degree of compression and upon the amount of scar tissue it contains. The right heart does not hypertrophy to any appreciable extent unless the pulmonary blood-pressure is definitely raised.

Experiments with lamp black have shown that the flow or stasis of lymph in the lungs is largely determined by the respiratory movements. It follows, therefore, that thoracoplasty determines a lymph stasis, and this is seen to be the case by examining microscopic sections of such lungs: the lymph vessels are markedly dilated and there is great deposition of pigment around them. As stated above, this stasis prevents dissemination of bacillary emboli to unaffected parts of the lungs, and checks the constant "tuberculinization" of the system with the toxic products of the tubercle bacilli; it is this action which is chiefly responsible for the rapid

clinical improvement of patients after pulmonary compression. Stasis of toxic lymph is believed to be responsible for the stimulation of the connective tissue to grow and encapsulate the tuberculous lesions.

Saugmann has spoken of the compressed lung being emptied of its waste products "like a pressed sponge." The elimination of excess tubercle bacillus-carrying secretions from the bronchial tree, and from cavities eliminates one of the most dangerous sources of spread of infection in advanced tuberculosis. Once the loose exudate and semisolid masses are squeezed out much inflammation quickly subsides. Even maximum compression flattens only the alveoli and small-medium sized bronchi; those bronchi protected by heavy cartilage remain open, and, as the pulmonary parenchyma contracts with fibrous tissue, they tend to bronchiectatic widening. Sometimes, however, new fibrous tissue will work in between the mucous membrane and cartilage of the larger bronchi and fill their lumina.

Examination of a compressed lung, which has successfully controlled its tuberculous lesions, shows a fleshy mass, full of connective tissue which is particularly evident around the blood and lymph vessels and bronchi, and as septa radiating from the subpleura. Some of the bloodvessels may be thrombosed. The tubercles are dry, and are seen to be firmly encapsulated by fibrous tissue which either just surrounds them or grows through and through them. If any new tubercles are found, which is rare, they are small, noncaseous and contain many giant cells. Von Muralt says that the healing effect of pneumothorax compression is sometimes so permanent that if an arrested case later becomes actively tuberculous, the disease may be entirely in the formerly better (uncompressed) lung!

These favorable effects of compression are apt to be seen only upon disease that is predominantly proliferative or fibrous in character, as the connective tissue for the encapsulations seems to arise largely from that which has already formed in an unsuccessful attempt to cure. As there is little tendency toward connective tissue formation in exudative lesions, lung compression is less likely to be followed by fibrous encapsulation.

Ample necropsy material has shown that the amount of connective tissue in a compressed tuberculous lung is far in excess of that in an uncompressed, tuberculous lung, and that it will form in cachectic persons in whom it could not be expected, were the lung uncompressed. Henschen asserts that the amount of new connective tissue roughly corresponds with the degree of compression, and, of course, with its duration. Factors responsible for the growth of fibrous tissue in compressed lungs are: (1) stimulation by toxins in the stagnant lymph; (2) chronic hyperemia; (3) cessation of lung function.

(To be continued)

THE USE OF RADIUM RADIATIONS IN THE TREATMENT OF TONSILS: A FURTHER REPORT.*

By Francis H. Williams, M.D.,[1]
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The problem of caring for the tonsils deserves careful study, because of disease in these organs themselves and of the complications in other parts of the body, originating in the tonsils, that diminish the well-being and economic value of a large number of persons.

The fact that lymphoid tissue, particularly when diseased, is easily acted upon by radium makes this remedy of especial value for treating the tonsils or other lymphoid tissue in the throat. Judging by the tests kindly made for me by Dr. F. H. Slack, a director of the Sias Laboratories, Brookline, Mass., the results obtained by the use of radium when short exposures are made are not due to a bactericidal action of this remedy. In these tests the cultures were exposed twenty minutes to 38 mg. of radium element placed at a distance from them of 0.25 cm., the filter used being of aluminum 0.29 mm. thick. Dr. Slack reported as follows: "I exposed freshly planted cultures of Staphylococcus pyogenes aureus and of Streptococcus viridans to the action of your radium for twenty minutes each. It had no inhibitive action at all upon the growth of these bacteria, the exposed cultures and the controls growing equally well."

My method of treating the tonsils with radium is carried out with instruments that I have devised for the purpose, by means of which the desired amount and quality of the radiations[2] may be applied under good illumination to the parts to be treated while the other parts are shielded.

Container, Diaphragms and Filters. The container (Fig. 1) is made of gold, because the amount of radiations penetrating a suitable thickness of this heavy metal is small, and has an aluminum cover, 0.29 mm. thick, that allows many times as much radiation to pass through it as does the gold portion of the instrument. The container is so made that when its position is changed the radium

* Read by title at a meeting of the Association of American Physicians, May, 1923.

[1] Treatment of Hypertrophied Tonsils and Adenoids by Radium: A Preliminary Statement, Boston Med. and Surg. Jour., 1921, **184**, 256. The Treatment of Tonsils by Radiations from Radium Salts Instead of Operation; 101 Cases, Trans. Assn. Am. Phys., 1922, **37**, 204; Boston Med. and Surg. Jour., 1922, **187**, 412. Traitément de l'hypertrophie amygdalienne par la curiethérapie, Paris méd., 1923, **47**, 110.

[2] It is important for the general practitioner to distinguish between the radiations and the emanation from radium. The radiations are given off uniformly for centuries, whereas the emanation, which is collected in a laboratory, loses one-half of its strength in four days.

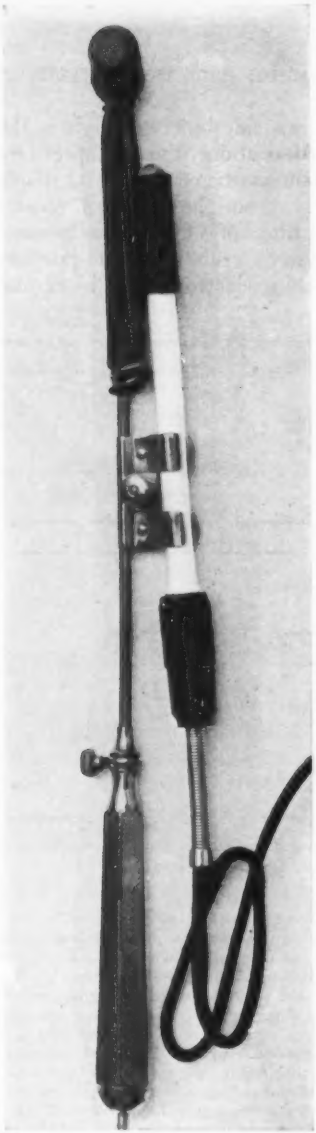

FIG. 1.—(About ½ length.) General view of the instrument used to apply radium. At one end is the container (see also Fig. 2 *C*) and at the other the handle. If the screw binding the handle to the rod is set in line with the front of the container the direction of the rays issuing from the latter can be additionally noted. A rubber cot, a fresh one is used for each patient, covers the container and part of the rod and is kept in place by an elastic band at either end. The glass tube carrying the electric lamp is held firmly between double-spring clamps, designed for the purpose, bound to the rod by another clamp by turning a nut. Red rubber tubing (black is too translucent), to exclude the light, covers the lamp except at its very end. A fresh piece is used for every patient. As the lamp and the container move together, the portion of the throat to be treated and the container receive a good illumination, the intensity of which may be varied by adjusting the special rheostat (not shown in cut) which controls the lamp. The current may be turned off from the lamp by giving its hard rubber socket at the end of the wire a half-turn to the left.

does not settle to one side but remains in a thin, uniform layer.[3] From the front of the container the rays spread out like an open fan, but their distribution can be controlled by diaphragms of different sizes and shapes (Fig. 2) and the amount of radiation limited and the quality modified by filters of different thicknesses. Thus the gamma rays only may be used or a mixture of the gamma and the beta rays, more properly speaking electrons, may be employed, the electrons,

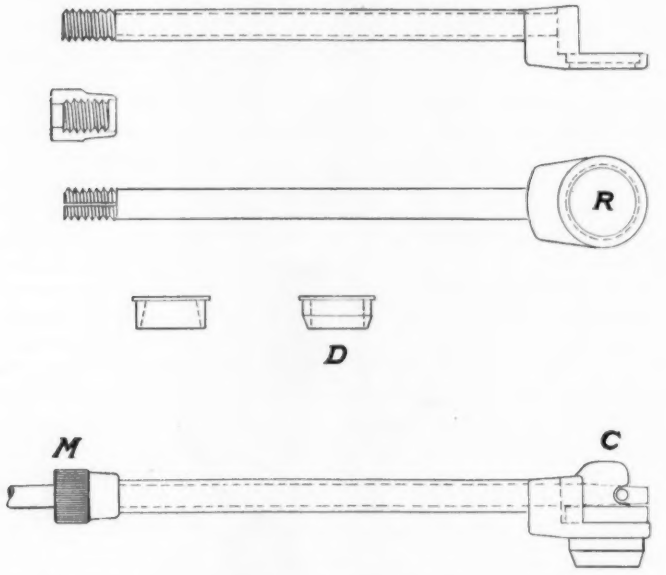

FIG. 2.—(Full size, except the tube, which is ½ inch longer.) This figure shows the method of holding the diaphragms which may be of various shapes and sizes, as occasion requires, and two of which are shown (see *D*). The filters—not shown—are disks of aluminum, and they and the diaphragms are held in the ring *R*. This ring also acts as a large diaphragm to prevent too much spreading of the rays. *C* is the container, and on its left is a mass of gold, also seen to the left of *R*, which still further prevents the radiations from issuing in the direction of the handle. *M* is the nut with a milled head that clamps the split end of the tube, which carries the diaphragm and the filter, to the rod, at the end of which is the container. To fasten the container securely to the rod a ring of wire about 10 mm. in diameter, ¼ part of which has been cut off, is passed through the small hole on the rod (shown below *C*) and then folded back onto the top of the container. To change the filters or the diaphragms, the handle and clamp must be taken off the rod. Failure to confine the action of the radium to the tonsils by an appropriate diaphragm would give rise to irritation for a time in adjacent parts, in the pillars, for example. When the radium is to be used in the upper part of the pharynx, a higher diaphragm than that shown at *D* should be employed, in order to protect the soft palate. When the container is not in use its front is covered by a thick disk of gold held in the ring *R*.

[3] I wish to express my thanks to Prof. Frederick G. Keyes for his kindness and resourcefulness in having these conditions fulfilled.

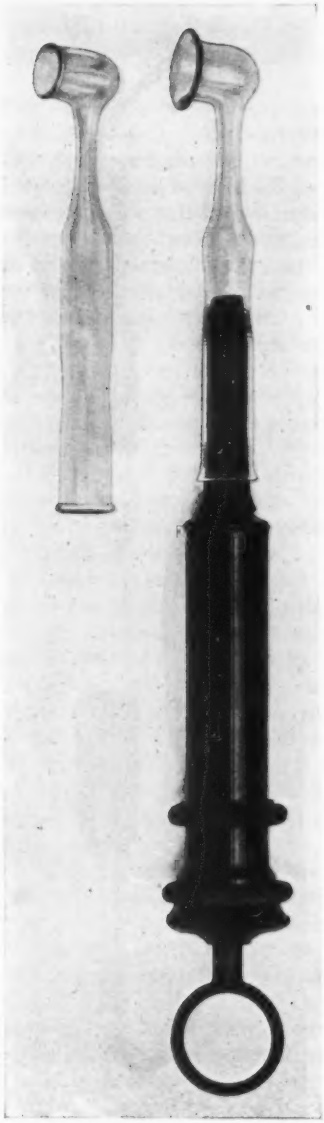

FIG. 3.—(Two-thirds size.) This figure shows an evacuator used to find out whether or not there is anything in the tonsil that can be drawn out. It consists of a hard-rubber ¾-ounce (25 cc) syringe, the piston of which slides easily. In order to make an air-tight joint between the glass tube and the syringe the tube has been thickened about 1 inch from the end, thus its caliber has been made a little smaller. A piece of pure rubber tubing covers the entire nozzle of the syringe. After this tubing has been moistened the nozzle of the syringe is pushed gently into the glass tube a little beyond the first constriction, where it is held firmly like a cork in a bottle. The diameter of this tube just below the cup, as shown in the figure, is too small. The cup may have openings of different sizes and shapes—oval as well as round—to fit a given tonsil. The glass tube can, of course, be thoroughly sterilized. It should not be left on the syringe after it has been used, as if left it might become too firmly attached.

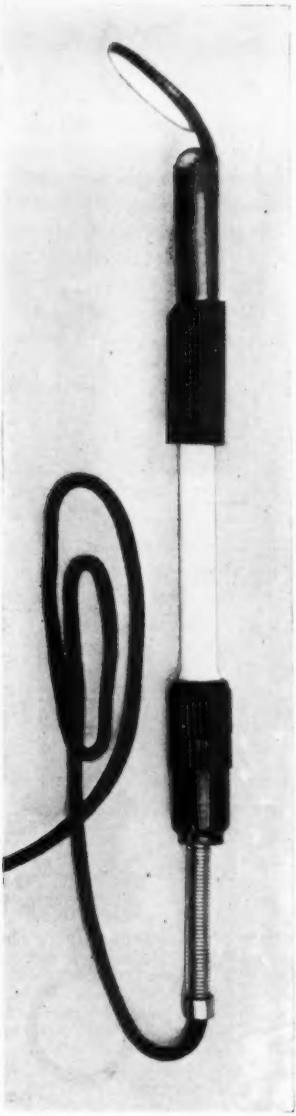

FIG. 4.—The laryngeal mirror. The backing of the mirror is of pure silver and there is no paper between the silver and the mirror. Opposite its lower portion is an electric lamp, covered for a short distance, except at the very end, with a pure silver tube split lengthwise, which is continuous with a broad band of pure silver attached to the back of the mirror. The heat from the electric lamp is conducted by this silver tube to the silver backing of the mirror, and thus the latter is kept at such a temperature that moisture from the patient's breath is not condensed on it while the laryngeal examination is going on. It is necessary that pure (not sterling) silver be used, otherwise the conduction of heat from the lamp to the mirror would be insufficient. A piece of red rubber tubing, pulled back in order to show the silver tube underneath, is cut off at one end at an angle of 45 degrees, in order to obstruct as little as possible the observer's complete view of the mirror. At the other end of the lamp there is a socket and cord attachment.

when so desired, being in such a large proportion as to make the amount of the gamma rays negligible. As the electrons have different degrees of penetrating power and the less penetrating ones are in larger proportion, the latter must be shut off by a suitable filter when the deeper tissues are to be acted upon, otherwise the tissues near the surface will receive too much radiation. The so-called alpha rays need not be considered, as they are prevented from escaping by the cover of the container. When the container is to be used for other purposes than the treatment of the faucial tonsils —lingual tonsils, for instance—it should be taken off the straight rod (shown in Fig. 1) and attached to a rod that has been bent, about 1 cm. from the end, to the angle best adapted for allowing the rays to reach the given part. The container is usually held directly against the faucial tonsil, but when used for treating adenoids, lymphoid tissue in the pharynx,[4] the lingual tonsil or the region near the Eustachian tube, for example, it should be held near but need not touch them. The two containers I generally use hold 26 and 38 mg. of radium element respectively.

Electric Lamp. The electric lamp (Fig. 1), which gives a strong light, is covered near the end by a piece of red rubber tubing (black is too translucent), which excludes the light except at the very end where it is needed and is clamped to the rod carrying the container. The lamp and the container move together, and both the container and the portion of the throat to be treated receive a good illumination, the intensity of which may be varied by adjusting the rheostat that controls the lamp.

Evacuator. This instrument (Fig. 3) is used, if pressure is not sufficient, to see whether or not anything that it is desirable to get rid of can be drawn out of the tonsil.

Laryngeal Mirror. This mirror (Fig. 4) may be first warmed by holding it over a lamp, but after being put into the throat the electric lamp attached to it keeps it warm enough to prevent the condensation of moisture on its surface from the patient's breath, but at the same time not warm enough to be uncomfortable for the patient. The backing of the mirror and the tube surrounding the upper part of the lamp and the broad band connecting the two are of pure silver (the conduction of heat would not be sufficiently good if the silver were only sterling) and there is no paper between the silver and the mirror. I have found it useful for examining lingual tonsils and the larynx.

Tongue Depressor. Figure 5 shows a common form of tongue depressor with an electric lamp attached, the light from which is excluded except where it is desired. If a broader tongue depressor

[4] When treating lymphoid tissue on the walls of the pharynx the aluminum cover (0.29 mm. thick) of the container makes a suitable filter and the treatments given should be about five minutes when 38 mg. of radium element are used.

is needed the lamp may be taken off the rod, as shown in the cut, and put on the other rod.

Timing Exposures. As it may be necessary to interrupt the treatment—to allow the patient to swallow, for instance—a stop watch, such as is used in football games, is useful as it permits the total length of the treatment to be accurately registered.

Treatment (Fig. 6). The treatment may be so moderate as to produce no discomfort in the tonsils or so vigorous as to cause some irritation there for a few days. There may be reasons, especially from the patient's point of view, for choosing one or the other of these ways. When 38 mg.[5] of radium element are employed, about

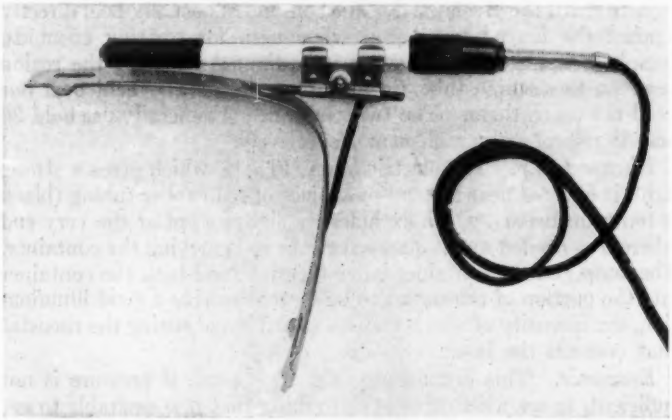

FIG. 5.—A common form of tongue depressor, with attachment for holding an electric lamp, the light from which is excluded except in the direction of the object it is desired to examine. If a broader tongue depressor is needed the lamp may be taken off the rod, as shown in the cut, and put on the other rod.

ten minutes for each tonsil, with a filter of aluminum 0.58 mm. thick, is a good first dose for an adult; a somewhat longer exposure may be given if the filter is 0.87 mm. thick. Subsequent doses should be smaller or larger as the conditions require, usually not exceeding fifteen to twenty minutes, the average number necessary being about four treatments, when aluminum filters 0.58 mm. or 0.87 mm. thick are employed, given ordinarily at intervals of about three to four weeks. If the same amount of radium element and the same filter and diaphragm are employed and the same length of exposure made, a given dose may be repeated with exactitude.

[5] With the experience I have now had in the treatment of tonsils, I feel justified in using a larger amount of radium with the object of shortening the length of each treatment and the duration of the whole treatment.

Conditions vary widely in different patients, therefore the amount and quality of the radiations to be applied can be determined only by experience, and with this as with every new method care should be taken not to carry the treatment too far. In cases where the tonsils are very large a longer treatment than is necessary for the average case is desirable. A day or two after such a treatment, instead of the ordinary discharge a profuse one that may last for several days may follow, and the throat may be sensitive for a few days when cold, hot or highly seasoned food is eaten. The com-

FIG. 6.—This cut shows a patient reclining comfortably in a Morris chair. With the back at the angle shown in the figure the position of the patient affords the physician an excellent view of the throat and is convenient for the application of the radium. Further, in this position the saliva does not readily collect in the mouth. The seat of the chair, with its cushion, is 19 inches from the floor; if the patient is very tall, a cushion on the arm of the chair, under the elbow, may be desirable for the person applying the radium.

pensation for this is, as a rule, more rapid reduction in the size of the tonsils. Treatment should be continued while anything can be brought out of the tonsils by pressure or by the evacuator.

A good initial dose for children when 38 mg. of radium element are used, the aluminum filter being 0.58 mm. thick, is ordinarily five to ten minutes for each tonsil. For delicate children one treatment of even five minutes to each tonsil may produce such

improvement in their general condition that they will gain in strength and appetite, although there may not be much change apparent in the tonsils.

Should it be required, a freshly made 2 per cent solution of cocain may be used to desensitize the throat; or a large dose of bromides may be given some hours before the treatment, but this I have seldom found necessary. Patients have been instructed, if they have any discomfort after treatment, to use as a gargle a level teaspoonful of salt in a tumbler of water. During the stage of discharge, to obtain bactericidal action some non-caustic hypochlorite, such as chlorazene (about $\frac{1}{10}$ per cent solution) may be employed. Irritating applications such as argyrol, nitrate of silver, or the tincture of iodin should be avoided.

The 105[6] cases considered in this paper include 4 cases of lingual tonsils, and 101 cases of faucial tonsils that are divided into the following groups:

Enlarged tonsils	10
Tonsillitis	26
Tonsillitis and arthritis	17
Arthritis	14
Miscellaneous	21
Tonsillectomy (previous)	10
Tonsillotomy (previous)	3
Total	101

Enlarged Tonsils. The tonsils of these 10 patients have been reduced in size in varying degrees from one case in which there was but little tonsil left, to another in which there was great diminution in the right and some reduction in the left tonsil. This patient has had fewer colds since he had radium treatment.

W. A., aged three and a half years, was given three treatments to the right tonsil, with 38 mg. of radium element, the aluminum filter being 0.58 mm. thick, on December 16, 1922, and January 5 and 25, 1923, of five, five and seven minutes, respectively, and to the left tonsil on the same dates of five, five and eight minutes, respectively. On February 9 the tonsils could scarcely be seen; appetite had improved and she had gained 7 pounds. On April 4 she had one more treatment of eight minutes to each tonsil. When last seen, May, 1923, she was doing well. There was still something left of each tonsil.

April, 1924, her mother reported that she had improved very much.

T. L. E., aged thirty-one years, had very large tonsils and the cervical lymph nodes on both sides were affected. January 7, 1922,

[6] It is of interest to note that a considerable number of these patients were physicians, surgeons or members of their immediate families, or nurses.

a treatment of fifteen minutes was given to each tonsil with 26 mg. of radium element. Two days later the patient could swallow more easily. When seen again, on January 13, the tonsils and lymph nodes had diminished and there was some discharge from the crypts. February 9, the lymph nodes were no longer palpable; a second treatment of twelve minutes was given to each tonsil. No further treatment has been necessary.

Tonsillitis. The size of the tonsils has been reduced in the 26 cases giving a previous history of tonsillitis. When last heard from there had been no recurrence in 21 of these cases since radium treatment was begun. In the first and second of the remaining 5 cases the treatment was at first inadequate, and a recurrence taking place, further radium treatment was given. The first has had no second recurrence; the other had a slight attack ten months later, in August, 1923. The third patient, who had enormous tonsils, had an attack of tonsillitis during treatment, when the tonsils were partially reduced, following a long automobile ride on a chilly, windy spring day when she wore no hat. She was treated during the acute stage and improved more promptly than she had previously done from the attacks to which she had been subject at not infrequent intervals for years. The fourth case (W. J.) is given on page 28. The fifth case, that had a history of tonsillitis on the left side, was one of the early cases and was first treated with radium in March, 1921, and received less treatment than I now give. In October, 1923, a recurrence took place, but the attack was much lighter than those she had had before the use of radium and lasted only three to four days instead of a week or more.

A. J., aged twenty-seven years, had a history of repeated attacks of tonsillitis. The right tonsil was treated for fifteen minutes with 26 mg. of radium element on July 29 and August 27, 1922, respectively, and the left tonsil for fifteen minutes on July 29 only. There has been no tonsillitis during or since treatment.

H. C. H., aged twenty-five years, had a history of attacks of tonsillitis for years; the right tonsil extended one-half inch beyond pillars, the left a little beyond pillars. Three treatments were given to the right tonsil, one with 26 mg. and two with 38 mg. of radium element on May 24 and November 3 and 21, 1922, of ten, eight and eight minutes respectively, and two to the left tonsil, one with 26 mg. and the other with 38 mg. of radium element on May 24 and November 3 of the same year of ten and eight minutes respectively. April, 1924, he has had no tonsillitis since the first treatment was given.

I. W. H., aged twenty-six years, had a history of tonsillitis, with tonsils swollen, and a discharge for years, and has had poor health.

Three treatments were given to the right tonsil with 26 mg. of radium element of ten, five and ten minutes on February 24, March 13 and April 5, 1922, respectively, and two to the left tonsil of ten minutes each on February 24, and April 5, 1922, respectively. On April 8, the tonsils were well behind the pillars. On April 18, the patient had a severe cold in the head, but no tonsillitis with it.

Patient has greatly improved since the application of radium to the tonsils, and had had no return of tonsillitis when last heard from.

E. S. B., aged thirty-four years, had a history of tonsillitis every winter. The right tonsil was on a level with the pillars; the left extended three-sixteenths of an inch beyond the pillars. Four treatments were given to the right and eleven to the left tonsil in 1922 and 1923, the last on March 9 of the latter year. On March 30, the tonsils were found reduced in size. The patient has had no further trouble with them and is greatly improved in health.

February, 1924, there had been no return of tonsillitis.

W. J. History of one attack of tonsillitis yearly in February. On January 5, 1922, the patient was given a treatment of fifteen minutes to each tonsil with 26 mg. of radium element, and did not have the usual February attack. On April 19 she had a second treatment of ten minutes to each tonsil. Her work prevented her from keeping the further appointments given her, and I have been told that tonsillectomy was done in 1923, following an acute attack of tonsillitis.

Tonsillitis and Arthritis. There has been improvement in the general condition of these 17 patients and they have had no attacks of tonsillitis since radium treatment was begun with the exception of 1 patient. He had a slight recurrence three years after his first radium treatment and was again treated with radium. Relief from arthritis was obtained to a greater or less extent in all these cases; in 1 case there was entire relief from pain for seven months and then a recurrence took place (the patient failed to report four months earlier as directed), which yielded to further treatment (see Case H. M. A., page 30). In another case the temporary relief after radium was followed by another attack of arthritis, which suggests, judging by experience, that some other source than the tonsils should be searched for. The following case, given in a previous paper, is illustrative.

Miss Z. had recovered from an attack of arthritis but had an acute tonsillitis when I gave her radium treatment. After one application the tonsils were reduced to a very small size and she recovered from the tonsillitis. Four weeks later the patient had another attack of arthritis, a severe one, and tonsillectomy was

done without my being consulted, the small size of the tonsils facilitating the operation. In less than three weeks after this operation she had another attack of arthritis which was followed by still another in about four weeks. An *x*-ray examination was made at this time which showed abscesses around two of the teeth. The teeth were removed and three months later, when last heard from, she had had no further attacks of arthritis.

T. S. W., aged fifty-six years, had had sore throats for forty years, and tonsillitis perhaps a half-dozen times in his life. He had had an attack recently, which was followed by arthritis in knees that is diminishing. Five treatments were given to each tonsil, two with 26 and three with 38 mg. of radium element, the first on May 16, 1922. Subsequently he had a cold, neuritis, pharyngitis and laryngitis, but no tonsillitis. The right tonsil is below the pillars, with a flat surface; the left tonsil is on a level with the pillars. The arthritis is diminished.

F. G. K., aged twenty-one years, has a history of tonsillitis and has had considerable trouble with her feet, which is probably due to a mild arthritis. She has been advised by several physicians to have tonsillectomy done. The right tonsil is one-quarter of an inch and the left one-eighth of an inch beyond the pillars. Eleven treatments, the first on October 3, 1922, were given to the right and five to the left tonsil. The arthritis began to clear up after the first treatment, and she took off her arch supporters and has not worn them since. She has had no tonsillitis since radium treatment was begun. The right tonsil is flat; of the left, little remains.

K. F., aged forty-seven years, has had arthritis of the upper spine and occasional attacks of tonsillitis (a mild attack during winter of 1921–1922). In December, 1921, she had intestinal influenza, followed by arthritis of the knee, which was in splints for weeks. She used a wheeled chair, then crutches and now a cane. The tonsils are slightly beyond pillars.

April 22, 1922, she was given the first treatment, ten minutes to each tonsil, with 26 mg. of radium element, and reported three days later that she felt better. The second treatment, nineteen days afterward, was given to the left tonsil only. A week later her knees were better; she could walk better, go down stairs, and turn her head more easily. On June 29 the patient could go without a cane part of the time and her knee did not trouble her unless she exercised too much. She reported, "I have not had a particle of discomfort from the treatment, not even a scratchiness in the throat, as I might have had from a cold." Treatment was interrupted during the summer, then five more treatments were given to the right and four to the left tonsil.

Her general condition is very much improved and she is able to

go without a cane except when she walks on very rough places. The tonsils are apparently very small, behind pillars. April, 1924, she has had not tonsillitis since the beginning of treatment.

H. M. A., aged forty-two years, a district nurse, has had a history of repeated attacks of tonsillitis. She has had many colds and sore throats; and her throat was swollen and hoarse practically during the whole winter of 1921–1922. She recently has had pain in finger-joints and arm. She can get through her day's work, but is tired at night. Both tonsils three-eighths of an inch beyond pillars.

On May 11, 1922, she was given one treatment of ten minutes to the right tonsil and two of ten minutes each to the left tonsil on May 11 and 25 with 26 mg. of radium element. June 6, she reported great improvement in her health and strength and that she felt much younger. "I would not know anything had been done to my throat." She had no pain whatever in joints, elbows or fingers. She failed to report in September, as directed, because she felt perfectly well. On January 4, 1923, she had an attack of acute arthritis in her left elbow; the next day it was so swollen, painful and hot that she could not use her arm for telephoning. On January 5 she was given a treatment of fifteen minutes to each tonsil with 38 mg. of radium element, the aluminum filter being 0.58 mm. thick. On the 6th she was able to use her arm, comb her hair and dress herself. Further treatments with 38 mg. of radium element were given her, five to the right and seven to the left tonsil.

April, 1924, nearly two years since her first treatment, the patient reports that she has had no arthritis since the attack of January 4, 1923, and no tonsillitis since radium treatment was begun.

Arthritis. The arthritis diminished or disappeared in these 14 cases. Radium treatment may properly be given for alleviation as well as in the hope of permanent relief, or as a test if there is a doubt as to the origin of the arthritis. It may also be used as a test in other cases in which the diagnosis is obscure, but where the tonsils might be suspected, but in which tonsillectomy would not be justified. In acute arthritis improvement is often very prompt; in subacute and chronic cases it of course takes place more gradually. It is well to bear in mind that tonsils should not be disregarded as a source of arthritis because apparently they are not enlarged or because they are submerged.

C. E. F., aged forty-seven years, has always been very nervous and has had three nervous breakdowns. She has arthritis in hands, ankles and other joints. The tonsils are within the pillars, both apparently very small, but there is some discharge from the tonsils. On October 5, 1922, the first treatment of ten minutes to each tonsil with 26 mg. of radium element was given. On October 20, she reported that the arthritis was much diminished; there was no pain

in ankles or hands; appetite was improved; and a second treatment of ten minutes to each tonsil with 38 mg. of radium element was given. On October 26, arthritis was practically gone; she felt much better; and had been able to walk more during the past week than for the past two years. On November 21 felt fifteen years younger; and had no arthritis; a third treatment of five minutes to each tonsil with 26 mg. of radium element was given. On December 15 and 29 a fourth and fifth treatment, of eight and twelve minutes, respectively, was given to each tonsil with 26 mg. of radium element. January 5, 1923, the arthritis is gone absolutely. She has lost her extreme nervousness. Both tonsils are apparently very small. March, 1924, she is still free from arthritis.

M. C. D., aged fifty-seven years, has had neuritis for some time; and arthritis for ten days in right wrist. The tonsils are apparently rather small, well within the pillars. Two treatments were given to the right and left tonsils on October 21 and November 15, 1922, of ten and five minutes, respectively, with 38 mg. of radium element and a third treatment to the left tonsil on January 20, 1923, of ten minutes with 26 mg. of radium element.

The swelling began to go down and the arthritis was relieved within twenty-four hours. On January 26, 1923, no tonsil was visible, even when the plica was pushed aside. There was no arthritis or neuritis when last heard from.

P. F. had arthritis in feet, ankles, hands and wrists. The right tonsil was enlarged in its lower part, a little in front of the pillars. She has had treatments at long intervals, the first May 29, 1922, 10 to the right and 9 to the left tonsil in all, and has been greatly relieved.

This patient has been under direct observation; has gained steadily and now gets about her work without the great difficulty that she formerly had.

Miscellaneous. The tonsils of these patients, 21 in number, were treated with radium with satisfactory results, for a variety of causes, such as frequent colds, the relief from which was very striking, sore throats, sensitive throat with pain in the ears, neuritis and pain in the throat.

L. M. History: The patient cannot breathe through the nose; she has had an itching sensation in the throat for one or two years and colds all the time; the tonsils are within the pillars; the pharyngeal wall is rough.

November 14, 1923, a treatment of fifteen minutes was given to each tonsil with 38 gm. of radium element, the aluminum filter being 0.58 mm. thick, and a treatment of seven minutes to the pharynx, the filter being 0.29 mm. thick. December 6, she felt

better, the tonsils were smaller and were well within the pillars; a second treatment of fifteen minutes was given to each tonsil. January 8, 1924, she had a good appetite and had gained in weight, no treatment was given. February 8, the tonsils were still further within the pillars; a third treatment of fifteen minutes was given to each tonsil. April, 1924, she has had no colds since the use of radium.

H. L., aged seven years. Her physician thought there was risk of mastoid trouble if the tonsils were not cared for. She had been subject to earaches. The treatments by radium were as follows: December 8, 1921, fifteen minutes to the right and nineteen minutes to the left tonsil with 26 mg. of radium element, the aluminum filter being 0.87 mm. thick; January 7, 1922, fifteen minutes to each tonsil with the same amount of radium, but with an aluminum filter 0.58 mm. thick. The patient has had no earaches since radium treatment was given.

Lingual Tonsils. In treating lingual tonsils the container should be held on a rod the end of which has been so bent that the rays issue downward and forward and should be near but need not touch the tonsil. It is not well to push the treatment of lingual tonsils as rapidly as may be done in faucial tonsils, because all the food must pass over the tongue. The discharge that takes place some days after treatment may trickle down to the trachea and cause coughing. Should this happen, relief may be had by spraying the parts with peroxide of hydrogen, as washing off the discharge stops the cough temporarily. In one case the relief from constant cough at first was very striking, but later was less marked and treatment has not been continued; in the three others there has been continued improvement. More time and cases are needed to estimate the value of radium treatment for lingual tonsils.

Previous Tonsillectomy and Tonsillotomy.[1] Six of the 10 patients with a history of tonsillectomy and the 3 patients with a history of tonsillotomy had tonsillitis after these operations. There has been no recurrence since radium treatment was given.

B. E. C., aged thirty-one years, had tonsillectomy performed in 1919, but has had one or two severe attacks of tonsillitis every winter since then. She was advised to have a second operation, which she declined. She had a severe attack of arthritis before radium treatment. Three treatments were given to each tonsil, on February 12, March 5 and 19, 1923, respectively, with 38 mg. of radium element, the length of the treatments varying from eight to fourteen

[1] In this connection the following statement is pertinent: "A study of more than 30,000 patients from various sources one to four years after operation shows permanent results in only about one-half of the total number." Laura A. Lane, M.D., Associate Attending Surgeon, Eye, Nose and Throat Department, Minneapolis General Hospital; Minnesota Med., 1923, vi. 97.

minutes for the right tonsil and twelve to eighteen minutes for the left tonsil.

She has had no arthritis or tonsillitis since the first treatment. The right tonsil is almost gone, except for a small tab under the anterior pillar; the lower part of the left tonsillar fossa has a considerable amount of tissue in it.

S. H. H. had tonsils and uvula operated upon when four years old. She has very little tonsillitis, but catches cold easily. One treatment of ten minutes was given to each tonsil on February 1, 1922, and a second treatment of five minutes to the left tonsil on March 2 of the same year with 26 mg. of radium element.

Since radium treatment was begun she has had no tonsillitis, although she has had two colds and one attack of grippe. She feels well, better than she has ever felt. Both tonsils apparently are very small.

W. H. A., aged twenty-five years, had tonsillectomy performed in childhood, but has frequent attacks of tonsillitis. Three treatments were given to each tonsil of ten minutes each on June 10, July 13 and August 12, 1922, respectively, with 26 mg. of radium element.

The tonsils are well within the pillars. Subsequently he had a hard cold for a week, but no tonsillitis with it.

It is of interest to note that the tonsillar tissue left after tonsillectomy probably differs from that left after radium treatment. It is well to use radium before regeneration takes place.

The general condition of the patient improves, and the weight often increases after the use of radium. In a word, the whole picture may be altered by radium treatment. The patient may be changed from a tired, ambitionless individual to one with "pep," as patients often express it, and these results may be accomplished without irritation in the throat. In some cases great improvement has taken place in the general condition within two or three days before any change was apparent in the tonsils, for an explanation of this I think we must go to the biochemist, which suggests that we may do well not to lay too much stress on the necessity of their extirpation if there is improvement in other directions. How far it is desirable or necessary to reduce these organs in order to ensure no further attacks of tonsillitis, or of arthritis, of which the tonsils are the source, is yet to be determined. In nearly all these cases the tonsils have been reduced in size, but as a rule their complete removal has not been attempted. In some cases, after the treatment was completed, no tonsil was seen when a curtain, the edge of which was directed backward and which was attached near

the top of the anterior pillar and reached to near the base of the posterior pillar, was drawn aside; but when the finger was passed around the curtain, a flattened mass about as large as a good-sized pea was felt near the anterior pillar on the side toward the cheek. In such cases I should not expect that there would be any further trouble, but when the tonsils are not so reduced it remains to be seen after how long an interval, if at all, trouble will occur. Three of the 88 patients that make up the first five groups (the other 13 patients had had tonsillectomy or tonsillotomy before radium treatment was given) had tonsillectomy after radium treatment. The tonsils in the first case were large and fibrous, radium is not adapted to getting rid of the fibrous portion of a tonsil, and were removed for mechanical reasons; the tonsils in the second case were greatly reduced in size by radium treatment, but the patient had a sensation of something in his throat that caused him to swallow continually—I have not yet been able to learn whether or not his condition improved after tonsillectomy; the third patient, before radium treatment was completed (see W. J., page 28) had an acute attack of tonsillitis and tonsillectomy was done.

Conclusions. Radium is a valuable therapeutic agent not only for the treatment of faucial tonsils, but also for other lymphoid tissue in the throat.

The output of the radiations from radium is uniform in quantity and quality, therefore the dosage can be accurate; if the radiations used in a given case are adapted to the conditions present this remedy is an unusually safe one in careful hands.

This method of treating the tonsils with radium, so far as can be determined by an experience of over three years, evidently has advantages:

For cases that are not good operative risks.

For those in which tonsillectomy is incomplete, instead of a second operation.

For some cases in which the diagnosis is obscure.

In how large a proportion of the cases, for which tonsillectomy is ordinarily advised, radium should be used, time and further experience will demonstrate.

This method is also adapted to the treatment of lymphoid tissue in the pharynx and in the region near the Eustachian tube in cases of ear trouble.

There need be no delay in the use of radium on account of the season of the year, or because of acute conditions in the tonsils themselves, or of an acute stage in diseases that have their source in the tonsils.

There have been no harmful results from the use of this method in the more than 200 cases that I have treated, the first of them more than three years ago.

LIPOIDS IN 1000 DIABETIC BLOODS, WITH SPECIAL REGARD TO PROGNOSIS.

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(From the Clinic of Dr. E. P. Joslin at the New England Deaconess Hospital, Boston.)

The first anxious demand of the patient who has just been told that he has diabetes is apt to be: "What is the outlook, doctor? I want to know the truth." Very often a reliable reply could be offered only by a few physicians of special experience and acumen. For the rest of us who are treating the majority of the nation's million diabetics, reliance must be based on facts and more facts. Figures on the fat in the blood are strewn through case reports in the literature, but for practical guidance there is real need of a crystallization. It is most regrettable that the records of 10,000 lipoid analyses by Miss Mary Wishart[1] were lost during the war, since these with Dr. F. M. Allen's[2] clinical data on the same patients, might well, when critically digested, have thrown more light than can this series, which when subdivided yields groups often too small for entirely satisfactory numerical results. Two at least of the findings, however, justify this communication: (1) Diagnosis: The blood fat was abnormal with nearly the same constancy as was the blood sugar. (2) Prognosis: Most long-lived diabetics showed a blood fat less than 1 gm. per 100 cc.

Material. In the six years that have elapsed since my last study on blood lipoids in this clinic,[3] the value of the subject matter has been enhanced, in that a considerable number of cases have been closed by death, and the series has been enlarged by many new cases both completed and living. Of the total number of patients studied here, the proportion alive on June 1, 1923 was 71 per cent. The great bulk of observations were made before the advent of insulin. The observations will now be discussed under the same headings as formerly.

Definitions. As before, the term lipoids is used to cover any or all fatty substances: fatty acids, cholesterol, lecithin. Blood fat means those substances measured by Bloor's method[4] for so-called "total fat," namely, fatty acids plus total cholesterol but not lecithin.

Blood fat in whole blood will be the chief chemical analysis discussed in reference to each clinical aspect; in addition, under prognosis, cholesterol will be considered, both in whole blood and plasma.

The time of taking the blood samples was generally before breakfast, and also in general before the beginning of insulin treatment; the exceptions do not seem worth individual attention at present.

The first conclusion offered in the former paper was that the most satisfactory single determination for following a diabetic patient was Bloor's fat method, "total fat" as he called it, on whole blood. This method has since been depended on in this laboratory whenever a measure of the lipoids has been wanted. Done by a variety of hands, and during parts of the period done under unusual pressure of work, the results may be somewhat less comparable than those previously reported, but are believed adequate.

The notation per cent will be used so often to make prominent the frequency of occurrence of the various topics under discussion, that I believe clearness will be furthered by refraining from expressing chemical results in per cent. The biological chemists today appear to favor the notation mg. per 100 cc, but some have used gm. per 100 cc, and as this permits us to keep the decimal point in the same place as when saying per cent, this notation will be used throughout the paper.

There were 1062 blood samples, from 588 patients. The tables below will present sometimes the total of admission and later values consolidated, other times only admission values; sometimes figures from both living and fatal cases, other times from completed cases alone.

Relative Frequency of Various Levels of Blood Fat. First, let us recollect the highest normal blood fat reported:[4] 0.67 gm. per 100 cc. Now among our diabetics the commonest level was 0.7 to 0.8, occurring in 14 per cent of the blood samples, while in 60 per cent of the blood samples, the level was less than 1, and in 90 per cent less than 1.5 gm. per 100 cc. Higher levels occur with decreasing frequency, until we see that values of 1.8 or more occurred in only 7 per cent of the samples (Table I). These exceptional cases might repay special study.

Diagnosis of Diabetes from the Blood Fat. Particular attention was invited in the former paper to the regularity with which diabetes was accompanied by increased blood fat. There the values exceeded the normal maximum (0.67 gm. per 100 cc) 93 per cent of the time. In the present series abnormal blood fat was found in 78 per cent of the 1062 specimens, versus abnormal blood sugar (more than 0.11 gm. per 100 cc) in 72 per cent of the same specimens. If only the initial values be examined, the corresponding constancy of abnormal blood fat was 76 per cent, of blood sugar 82 per cent of the 588 patients. In making this count the blood sugar has been given the benefit of every doubt, because whenever the record was not clear as to whether the blood had been taken fasting, that has been assumed the case. This assumption is believed to favor the blood sugar because it is in general more markedly affected than the blood fat by a single meal. Conclusions that may be drawn are accordingly: On admission the blood sugar was abnormal somewhat more uniformly than the blood fat, but the reverse was true

after treatment. For diagnosis, therefore, the blood fat seems to be only slightly inferior to the blood sugar in untreated patients, and in treated cases somewhat superior. This greater stability of the blood fat at all events is worth consideration, even by those who still believe the more labile blood sugar to be more valuable.

TABLE I.—FREQUENCY OF VARIOUS LEVELS OF BLOOD FAT.

Blood fat, gm. per 100 cc.	No. of analyses.	All analyses, per cent.	
9.55	1	0.1	
8.90	1	0.1	
7.04	1	0.1	
6.30	1	0.1	
5.00	2	0.2	
4.00	3	0.3	
3.00	8	0.8	
2.90	3	0.3	
2.80	1	0.1	
2.70	6	0.6	7.2
2.60	4	0.4	
2.50	4	0.4	
2.40	4	0.4	
2.30	8	0.8	
2.20	8	0.8	
2.10	2	0.2	
2.00	9	0.8	
1.90	2	0.2	
1.80	8	0.8	
1.70	15	1.4	
1.60	17	1.6	
1.50	31	2.9	
1.40	29	2.7	
1.30	25	2.4	
1.20	53	5.0	
1.10	64	6.0	
1.00	103	9.7	
0.90	111	10.4	
0.80	139	13.1	
0.70	149	14.0	
0.60	122	11.5	
0.50	74	7.0	
0.40	38	3.6	
0.30+	16	1.5	
Total	1062	100.0±	

Dead Diabetics with Normal Blood Fats. With a normal admission blood fat yet now dead, there were 28 patients. Only 2 were mild, and they died of cardiorenal disease; 7 were of moderate severity; 19 were severe despite the low blood fats; 14 of them died in coma. In these 14 the interval between the blood fat and death was: Less than one year in 8, between one and two years in 5, and four and a half years in 1 case.

For the whole group of 28, the average interval between the normal blood fat and death was only 1.3 years. The average weight at the time of the fat analysis was 20 per cent under the normal standard. These last two facts again indicate that diabetes may

be severe despite a normal fat level. The best explanation that I can offer for the paradox is the submaintenance régime on which these patients presumably had been living prior to the blood analysis, a presumption suggested by the average dietary fat (known for 15 of them), namely, only 0.6 gm. per kilo, and the rather low blood sugar of 0.21 gm. per 100 cc.

To prove this explanation we need more observations on patients seen frequently over a period of years.

Duration of Disease before Blood Fat. The longer the duration the lower the average blood fat, as shown before,[3] and as confirmed by the amplified figures in Table II. The explanation offered is that patients who store up high blood fat are too severe to live long. The facts in Table II may be insisted on because they seem precisely contrary to the statement in the literature that the more long-standing the diabetic condition the more marked the abnormality in the blood lipoids.[4]

TABLE II.—DURATION OF DIABETES BEFORE BLOOD-FAT ANALYSIS.*

Duration, years.	No. of analyses.	Blood fat, average gm. per 100 cc.	
Under 1	49	1.01	
1 to 1.9	43	1.31	1.26
2	21	1.60	
3	5	1.89	
4	9	0.92	
5	10	1.03	0.97
6	14	0.95	
7	4	0.86	
8	4	0.87	
9	2	0.92	0.80
10	15	0.83	
20	4	0.72	
	180		

Prognosis. Can life expectancy be foretold from the blood-lipoids? An answer was sought in 1917 by an elaborate tabulation, but with scanty results owing to the short interval since the patients' discharge from hospital. A concrete reply has been achieved recently by Rémond and Rouzaud.[5] They found among 189 diabetics that 7 per cent had a plasma-cholesterol of 0.3 gm. per 100 cc or more, and that of these cases again only 7 per cent survived after the findings as long as two years. Their cholesterol danger line (Grigaut's technic[6]) corresponds to 0.43 gm. per 100 cc by Bloor's method, as nearly as I can judge from the average normals given by the authors of the respective methods: Grigaut 0.16 gm. per 100 cc and Bloor 0.23 gm. per 100 cc. Furthermore, it may be

* Unselected group of 180 specimens, admission and later, from both living and fatal cases.

well to remind ourselves that the highest cholesterols among the 20 normal bloods published by Bloor were 0.31 gm. per 100 cc on plasma and 0.25 gm. per 100 cc on whole blood. These explanations will help us now to understand certain of the groupings in Chart I

	LENGTH OF LIFE AFTER PLASMA-CHOLESTEROL ANALYSIS IN YEARS								
CHOLESTEROL g/100 cc.	0.1 or less	0.2–0.5	0.6–0.9	1.0+	2.0+	3.0+	4.0+	5.0+	6.0+
0.31 or less	··	⁘	⁘	⁙	⁘	··	·	···	▦
0.32–0.42		·	·	⁘	·	··	·		⁘
0.43–0.70	⁘		⁘	▦	···	···			⁘
0.71–2.20			⁘	·					

CHART I.—High cholesterol means bad prognosis. Each dot = 1 analysis.

and Table III (for plasma), and the table recently shown elsewhere[7] (for whole blood). These tables show that each successive group with higher cholesterol was characterized by a decided decrease in subsequent length of life.

TABLE III.—RELATION OF PLASMA-CHOLESTEROL TO PROGNOSIS.*

Plasma-cholesterol, gm. per 100 cc.	No. of analyses.	Length of life from blood analysis to death, or if alive June 1, 1923, years.
0.31 or less	64	4.1
0.32 to 0.42	15	3.1
0.43 to 0.70	38	1.8
0.71 and over (maximum, 2.2)	6	0.9
	123	

From Chart I it may be reckoned that the danger level of plasma-cholesterol was exceeded by 15 per cent of the patients, or 35 per cent of all specimens if we include both admission and later analyses; this shows the greater severity of these cases of Dr. Joslin's, as compared with 7 per cent in the series quoted.[5] Of his ill-fated group, 31 per cent lived more than two years, thus showing a happier outcome than (7 per cent) in the series quoted.

There are a few extraordinarily high plasma-cholesterols in the literature, which may be assembled here, translated where necessary into Bloor equivalents:

1.15 gm. per 100 cc (Grigaut[8]),

1.20 gm. per 100 cc (Rémond and Rouzaud[5]),

* Blood technic, with sodium ethylate; analyses by H. G.

1.35 gm. per 100 cc (Epstein and Lande[9]),
1.67 gm. per 100 cc (Bloor[10]),
1.71 gm. per 100 cc (Bloor[11]),
1.90 gm. per 100 cc (Bloor[12]),
2.11 and 2.20 gm. per 100 cc (present writer[3] on Joslin's Case No. 786 on two different days about nine months before coma; the simultaneous values on whole blood were 1.48 and 1.50 gm. per 100 cc).

Converse grouping by length of life, for 115 specimens on living and fatal cases (the latter 41 per cent of the 115) shows the same results (Table IV). For example, when the patient survived less than two years, the average plasma-cholesterol was 0.53 versus 0.3 when the patient lived more than two years.

TABLE IV.—RELATION OF BLOOD-CHOLESTEROL TO PROGNOSIS.

Length of life after blood analysis to death, or, if living, to June 1, 1923, years.	No. of analysis.	Cholesterol, gm. per 100 cc.			
		Whole blood.		Plasma.	
0.1 or less	6	0.38	0.41	0.48	0.53
0.2 to 0.5	6	0.25		0.27	
0.6 to 0.9	16	0.59		0.75	
1.0+	32	0.37		0.46	
2.0+	11	0.30	0.27	0.32	0.30
3.0+	7	0.37		0.45	
4.0+	2	0.25		0.28	
5.0+	4	0.20		0.22	
6.0+	30	0.25		0.28	
7.0+	1	0.21		0.25	

Prognosis from Blood Fat. Let us now return to the figures by the "total fat" method of Bloor on whole blood. Grouping the results according to the length of life subsequent to determination of the blood fat revealed little in my earlier paper but here makes plain the progressively longer expectation of life, the lower the blood fat. This rule holds whether we consider the admission values alone (patients), or both admission and later values together (all specimens).

For instance, if we group 351 specimens on fatal cases according to subsequent length of life, we find that when death occurred in six months or less, the blood fat averaged 1.15 gm. per 100 cc, when death occurred in from half a year to two years, fat averaged 1.03 gm. per 100 cc, if in more than two and less than four years the blood fat averaged 0.93 gm. per 100 cc, and if in more than four years the blood fat averaged 0.79 gm. per 100 cc. A table of these figures in greater detail may be found elsewhere.[7]

Or conversely, if groups are made according to the level of blood fat, it is again obvious that the greater levels are associated with progressively shorter lives, witness the averages in Table V, especially in the last column.

TABLE V.—RELATION OF BLOOD FAT TO PROGNOSIS.*

Blood fat, gm. per 100 cc.	Length of life after blood fat, years. Fatal; admission and later specimens consolidated.	Living; admission and later specimens consolidated.	Admission specimens; fatal and living specimens consolidated.	Later specimens; fatal and living specimens consolidated.	Grand total.
0.67 or less	(78) 1.2	(151) 2.8	(146) 2.5	(83) 1.9	(229) 2.3
0.68 to 0.99	(135) 1.2	(296) 2.4	(278) 2.2	(153) 1.8	(431) 2.1
1.00 to 1.49	(87) 0.9	(176) 2.1	(130) 1.7	(133) 1.6	(263) 1.7
1.50 to 1.99	(26) 0.9	(38) 1.7	(24) 1.2	(40) 1.5	(64) 1.4
2.00+	(4) 0.6	(27) 1.9	(12) 1.4	(19) 2.0	(31) 1.7 } (103) 1.5
3.00+	(2) 1.5	(7) 1.0	(2) 1.5	(7) 1.0	(9) 1.1
4.00+	(7) 0.7	(2) 0.3	(3) 0.8	(6) 0.5	(9) 0.6

(Parentheses enclose the number of specimens consolidated to obtain each average length of life.)

* Whole blood, Bloor's "total-fat" method. Highest value among 20 normal bloods (Bloor) was 0.67 gm. per 100 cc.

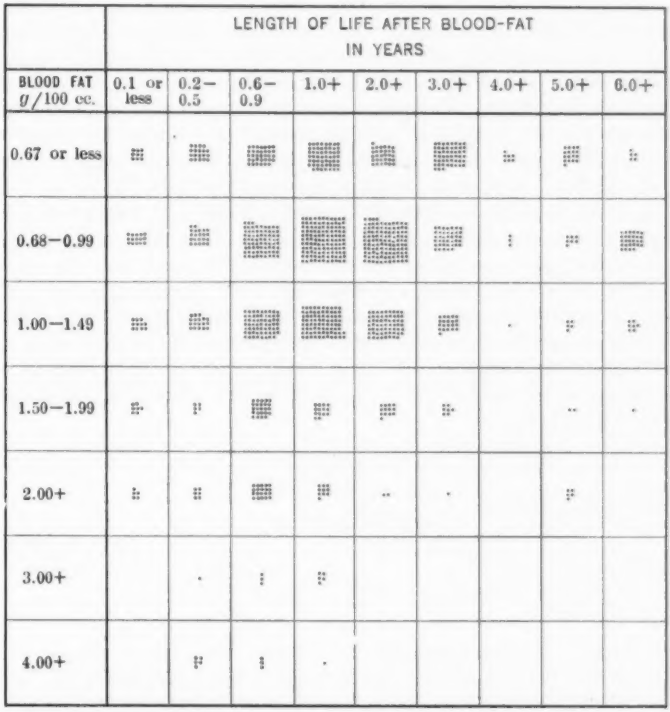

CHART II.—High blood fat means bad prognosis. Each dot = 1 analysis.

The frequency distribution is plotted in Chart II. Among many combinations there visible, according to one's interest, note that when a blood fat turned out to be 2 gm. per 100 cc or more, the patient lived for less than two years in 86 per cent of such observations.

A high initial blood value, for sugar or fat, provided it yields under treatment to a value fairly near normal, may be thought of small import. The evidence given here indicates that a fall in the blood figure improves the prognosis for the average patient, but it does not prove that a fall in a particular patient renders his future as favorable as that of another patient whose value never was elevated. Furthermore, it seems hardly likely that such proof can be produced. On the other hand, a closely related but not identical possibility, which would be encouraging to patients with high admission values, seems logical enough to merit future study: A patient whose blood value starts at (say) three times normal but is reduced by faithfulness under treatment to nearly normal, may have a better prospect than a patient whose blood starts at only twice normal but remains there.

Weight at Time of Blood Fat. The evidence of this enlarged series, whether we consider only admission values on fatal cases alone (table recently published elsewhere[7]), or both admission and later values on both fatal and living cases (Table VI), confirms my earlier conclusions. Patients who at the time of taking blood were overweight or normal in weight showed a moderately elevated blood-fat level, with the normal weight blood fats averaging 12 per cent higher. The underweights, meaning patients 10 per cent or more below normal standard, showed a blood fat average of 1.13 gm. per 100 cc which is 40 per cent higher than the average blood fat of 0.81 gm. per 100 cc for the overweight diabetics. In other words, severe diabetics develop high fats simultaneously with emaciation. This rather paradoxical phenomenon is worth further study, perhaps in connection with observations: (1) In carcinoma, of increased blood cholesterol[13] (and blood sugar[14]); (2) in fasting, of increased blood lipoids[15] and (3) conversely in obesity—of decreased blood lipoids.[9]

TABLE VI.—RELATION BETWEEN BLOOD FAT AND BODY WEIGHT WHEN BLOOD WAS TAKEN.*

Weight of patient at time of blood, expressed in per cent overweight (+) or underweight (−), compared with medico-actuarial insurance tables of average weight for height and age.	No. of analyses.	Blood fat, average, whole blood (Bloor's method), gm. per 100 cc.	
+21 and over (maximum, +84)	44	0.83	0.81
+11 to 20	44	0.80	
+1 to 10	82	0.94	0.91
±0	4	0.75	
−1 to −10	116	0.90	
−11 to −20	147	0.94	1.13
−21 to −30	153	1.10	
−31 to −40	143	1.14	
−41 and under (minimum, −59)	64	1.60	

Broad normal

* All specimens, admissions and later, on both fatal and living patients.

Blood Sugar in Relation to Blood Fat. Increase of glucose in the blood is accompanied by increase of blood fat on the average (Table VII), though in individual patients a lack of parallelism is often puzzling.

TABLE VII.—RELATION OF BLOOD SUGAR TO BLOOD FAT.

Blood sugar (W. B., Folin), gm. per 100 cc.	No. of analyses.	Blood fat (W. B., Bloor), gm. per 100 cc.
0.11 and under	158	0.85
0.12 to 0.16	212	0.92
0.17 to 0.21	177	0.99
0.22 to 0.26	193	1.05
0.27 to 0.31	148	1.22
0.32 and over	104	1.16

Course of Blood Fat in Treated Diabetics. A progressive fall of blood fat under treatment, even with high fat diet, is conspicuous in Marsh's recent charts.[16] In the present series, among the fatal cases which had 3 or more fat analyses, the general slant of the blood-fat curve was downward in only 56 per cent, but upward in the remainder, that is in approximately half the cases.

If a composite curve be made by averaging such blood-fat values as were taken on admission, those one week later, and so forth, we

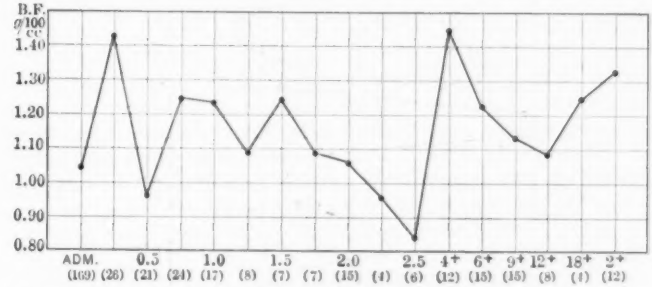

CHART III.—Course of blood fat in treated diabetics. Interval after admission, in months. Fatal cases. (Parentheses enclose number of blood fats averaged for each plotted point.)

get Chart III. The plotted averages are disappointingly irregular in distribution, very possibly because of the small number of cases represented by some of the averages. The general aspect of the curve, however, suggests the following tendencies in the behavior of the blood fat:

1. Abrupt rise consequent on beginning of treatment by severe sub-maintenance diet. This may be fundamentally related to the rise in lipoids after fasting, as noted elsewhere.[15]
2. Fairly regular fall during about the first three months thereafter.
3. Irregular but definite rise during subsequent life till death.

If a curve be plotted from an unusually long series of blood fats on a patient who has seemed accurate and faithful the same tendencies appear (Chart IV):

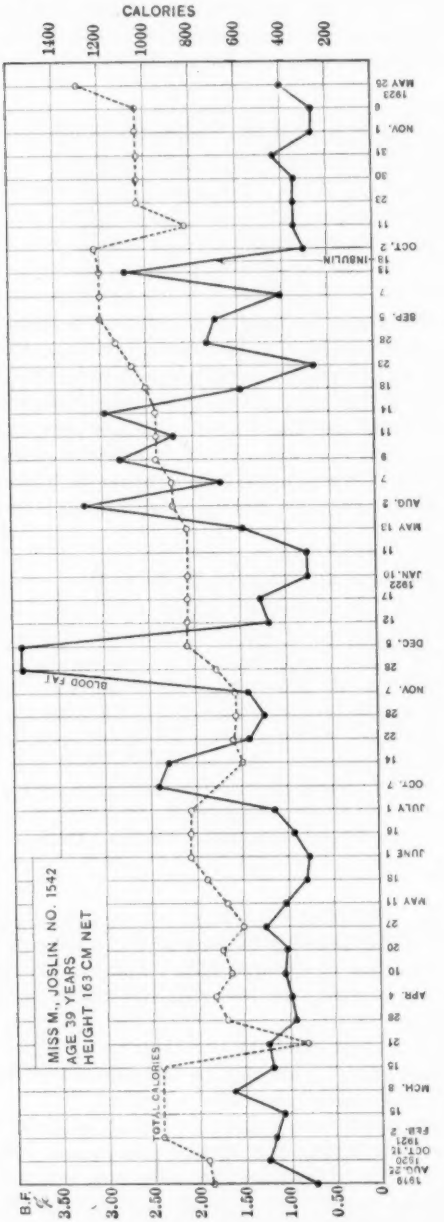
CALORIES
1400
1200
1000
800
600
400
200
B.F. %
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0
MISS M., JOSLIN NO. 1542
AGE 39 YEARS
HEIGHT 163 CM NET
TOTAL CALORIES
BLOOD FAT
INSULIN
1919 AUG. 22
OCT. 12 1920
FEB. 2 1921
MCH. 8
15
21
28
APR. 4
10
20
27
MAY 11
18
JUNE 1
16
JULY 1
OCT. 7
14
22
28
NOV. 7
28
DEC. 5
12
17
1922 JAN. 10
11
MAY 13
AUG. 3
7
8
11
14
18
23
28
SEP. 5
7
18
OCT. 2
11
23
30
31
NOV. 1
6
1923 MAY 25

CHART IV

1. Rise at first 0.75 to 1.65 per cent, average of 5 values being 1.18 per cent.

2. Fairly regular fall later for about four months, minimum 0.8 per cent and average level for 12 observations being 1.03 per cent.

3. Irregular but definite rise during ensuing year (October 1921–October 1922); peak 3.85 per cent and average of 23 determinations being 1.92 per cent.

4. Then the advent of potent insulin produced a beautiful fall and flattening of the curve below the danger level of 1 per cent, the average for 8 analyses being 0.85 per cent. Insulin effect is the more picturesque because during this period the total calories are only a little lower than during the preceding period of severely high blood fats.

5. The astounding fluctuations during the severe stage appear to have been correctly observed, in view of the duplicates both at the highest (Nov. 28 and Dec. 5) and at the lowest points (January 10 and 11). At the same time these fluctuations can not be now explained from the recorded calories, fat, carbohydrate, or general condition of the patient. Solution seems to demand the most precise technic, together with more frequent determinations (probably daily) than hitherto usually made.

Summary. A plea is made for more use of statistics in prognosis.

The blood fat (and cholesterol) in a considerable series of diabetics is studied in regard to the relative frequency of various levels of blood fat, diagnosis, duration of disease before fat determination, duration afterward (= prognosis), body weight, blood sugar, course of blood fat under treatment.

Frequency distribution: Strikingly high blood fats are astonishingly infrequent, for example, of 1062 blood samples, 90 per cent had blood fats below 1.5 gm. per 100 cc.

Diagnosis. The blood fat is above normal with a consistency equal to the blood sugar, for example, of the 1062 samples 78 per cent had blood fats above 0.67 gm. per 100 cc, which is the high limit of normal; while 72 per cent had blood sugars above 0.11 gm. per 100 cc before breakfast, which is taken here as the high limit (if you prefer as a limit 0.12 or 0.13, the blood sugar will make a worse showing).

The diagnosis of renal glycosuria, as well as of diabetes mellitus, may be materially aided by a blood fat. Hornor[17] has suggested that renal glycosuria may be ruled out whenever the blood fat is excessive, certainly if over 1 gm. per 100 cc.

The longer the duration of the disease before examination, the lower the blood fat, presumably because only those patients live long who have low fats, that is, mild diabetes.

Prognosis. Two years has been suggested as a convenient limit to use for a general statement. The cases in this series to achieve this length of life had blood fats averaging less than 1 gm. per 100 cc. When the fat exceeded 2 gm. per 100 cc, the patient lived less than

two years in 86 per cent of the instances. Detailed tables demonstrate the rule that progressively each group with a higher blood fat level (or similarly with higher cholesterols) is characterized by a distinctly shorter life expectancy.

Body weight: Underweight diabetics, that is, the severe cases of denutrition (10 per cent below standard), showed blood fats 40 per cent higher than the fat diabetics, the mild cases.

Blood sugar parallels blood fat more in averages than in individual cases.

The course of the blood fat under treatment is less easily interpreted than the blood sugar and needs further study.

All in all, blood-fat analyses are a material aid in the diagnosis and especially the prognosis of diabetes mellitus, and therefore where a laboratory is at hand deserve to be done, at least on admission of every patient.

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SPLENECTOMY, ITS END-RESULTS AND CLINICAL INDICATIONS.

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Interest in the subject of splenectomy has for more than a decade centered largely about the subject of pernicious anemia. Its benefits in that disease are still largely problematical and time has decreased rather than augmented the enthusiasm for it. Among physicians the discouraging results of splenectomy in pernicious anemia have brought about an undeserved distrust of splenectomy in general. This is unfortunate, for there surely are conditions in which the procedure is of the greatest value. With the object of showing what may be expected in properly chosen cases, the present brief series is reported.

Case Reports.—Rupture of Normal Spleen. Case I.—E. C., male, aged thirty-four years. This previously healthy man was brought to the Boston City Hospital on November 28, 1908, immediately after having been injured in a railroad accident. Dr. F. J. Cotton removed the ruptured spleen. There was much blood in the abdomen. No transfusion was done either before or after operation.

About ten months later a lymph node could be felt in the left neck and later another in the groin. These gradually subsided and there was never anything resembling general glandular enlargement. Except for slight backache and vague pains in the upper abdomen in the first year or two after operation he has remained perfectly well.

Unfortunately this spleen was not examined microscopically, but there is no reason to suppose that it was diseased.

This is the only case of removal of a normal spleen in this series. The continuance of health after splenectomy is in agreement with the observations of many other writers. The blood changes differ from those found clinically and experimentally by certain workers, but comment on the matter will be deferred until later in this paper.

Five Cases of Splenic Anemia. Case II.—R. C., female, aged thirty years, an Italian woman, who had for three years noticed a tumor low down in the left abdomen, slowly increasing in size. It was somewhat painful and there was an indefinite story of debility, dyspnea and nosebleed. She was operated upon by Dr. C. G. Cumston, March 29, 1904. The tumor proved to be a greatly ptosed spleen, weighing about 450 gm. (the normal is 150 to 250 gm.).

CASE I.—SPLENECTOMY FOR TRAUMA, NOVEMBER 28, 1908.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.				
				Polymorphonuclear neutrophiles.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.
Dec. 15, 1908	89	4,048,000	8700	69.9	21.6	4.5	2.7	1.0
" 31, 1908	99	5,200,000	7800	64.7	22.6	7.1	4.2	1.2
Jan. 29, 1909	100	5,184,000	9300	48.4	37.1	6.9	6.0	1.4
Apr. 7, 1909	101	5,568,000	7200	37.0	47.3	9.8	3.4	1.2
June 14, 1909	105	5,352,000	5100	52.5	34.0	9.0	3.5	1.0
Oct. 4, 1909	110	4,936,000	4900	55.9	27.9	11.5	3.7	0.7
Jan. 11, 1910	112	5,204,000	7550	59.9	29.9	5.5	3.6	0.9
May 19, 1910	114	5,669,000	7400	53.7	34.5	7.8	2.7	1.0
Nov. 14, 1910	121	6,112,000	6300	56.8	30.4	7.6	3.2	2.0
Apr. 5, 1911	103	5,200,000	8000	59.0	26.0	12.0	1.0	2.0
Oct. 18, 1921	93	5,004,000	8200	62.6	23.4	8.4	5.8	0.8

Oct. 18, 1921: Platelets, 152,000; hemolysis in NaCl solution begins at 0.375 per cent and ends at 0.275 per cent.

No Howell-Jolly bodies, nucleated red cells or myelocytes were seen in any of the smears examined.

CASE II.—REMOVAL OF ENLARGED AND DISPLACED SPLEEN, MARCH 29, 1904.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.				
				Polymorphonuclear neutrophiles.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.
Mar. 30, 1904	75	5,680,000	13,800	82.6	6.2	9.0	2.0	0.2
Apr. 6, 1904	80	6,488,000	7,700	52.7	15.0	13.7	18.0	0.6
" 12, 1904	..	....	...	65.0	15.0	16.0	4.0	0.0
" 18, 1904	...	5,680,000	10,600	48.8	9.2	16.4	24.8	0.8
May 4, 1904	70	4,896,000	11,500	58.0	13.5	10.0	17.5	1.0
Aug. 5, 1904	80	4,900,000	14,400	65.0	11.7	11.7	11.0	0.6
Sept. 9, 1904	70	4,752,000	10,750	52.0	20.6	7.4	18.4	1.6
Nov. 30, 1904	90	5,208,000	7,400	40.4	25.9	13.4	19.5	0.8
Mar. 22, 1905	95	4,584,000	10,800	64.6	13.9	11.0	10.3	0.2
Nov. 24, 1905	85	4,636,000	13,200	64.8	19.7	7.6	7.6	0.3

No myelocytes or nucleated red corpuscles in any of the smears.

Five months after operation she had a sore throat, accompanied by slight, general enlargement of the lymph nodes, which subsided promptly. There was some complaint of pain in the upper abdomen

and back, and twice it was noted that the gums were red and somewhat swollen. Otherwise she remained in good health throughout the period of observation, twenty months.

Sections of the spleen have recently been examined by Dr. F. B. Mallory, who reports as follows: Capsule, thin; trabeculæ, slender; arteries and lymph nodules, negative. Blood sinuses were very distinct and the walls were thickened, showing that stroma of the pulp is increased in amount. No eosinophiles found. Numerous polymorphonuclear and endothelial leukocytes in the blood sinuses. Diagnosis: Chronic splenitis.

CASE III.—E. B., male, aged fourteen years, came under observation in January, 1905. There was a history of pallor, fatigue, dyspnea and pain in the left side for at least three years. The liver was normal, the spleen 3 cm. below the costal margin. There were small lymph nodes in axillæ and groins. The degree and type of anemia is shown in the table. During the three years that preceded operation his weakness and disability slowly increased. Both nodes and spleen became larger, the latter finally reaching 9 cm. below the ribs. Sexual development was retarded and at the age of seventeen years, the breasts were large; there was no axillary and little pubic hair, and erections had not occurred.

CASE III.—SPLENECTOMY FOR BANTI'S DISEASE, MARCH 25, 1908.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.				
				Polymorphonuclear neutrophiles.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.
Jan. 23, 1905	60	3,244,000	6,100	77.6	15.2	4.4	2.0	0.8
Mar. 16, 1905	70	4,152,000	6,200	63.8	20.2	7.2	7.4	1.4
July 3, 1905	65	3,080,000	5,900	69.4	21.0	6.3	3.3	3.0
Aug. 14, 1906	60	3,256,000	15,870	81.7	10.0	6.3	2.0	0.0
Aug. 19, 1907	50	2,704,000	10,700	71.4	18.7	5.0	4.2	0.7
Mar. 3, 1908	62	3,160,000	9,900	75.0	18.6	1.7	3.7	1.0
" 15, 1908	76	3,516,000						
" 26, 1908	88	3,798,000	38,000	88.6	3.1	8.1	0.0	0.0
" 30, 1908	89	4,416,000	15,700	69.6	21.5	6.2	2.7	0.0
Apr. 10, 1908	93	4,800,000	27,400	63.8	25.9	6.0	2.8	1.5
" 30, 1908	104	5,080,000	11,600	66.5	18.6	7.6	6.3	1.0
July 28, 1908	99	5,008,000	16,600	53.2	25.2	5.7	14.7	1.2
Aug. 11, 1908	100	....	17,000					

Splenectomy was done, March 25, 1908, by Dr. Hugh Cabot. After a somewhat stormy convalescence he showed most marked and

gratifying improvement. His color improved, and, in two weeks the anemia, which had resisted treatment by iron, arsenic and other medical means for three years, had disappeared. He remained well until August 10, 1908, four and a half months after operation when he died of acute appendicitis.

Autopsy by Dr. Mallory showed general peritonitis and bronchopneumonia. The mesenteric lymph nodes were enlarged and firm, Peyer's patches slightly reddened. The bone-marrow was red. The liver weighed 1425 gm.; microscopically it was normal. Spleen (removed at operation, four and a half months before death), capsule thin, trabeculæ slender and not numerous; arteries and lymph nodules negative. Blood sinuses distinctly outlined. Stroma between them moderately increased in amount. Eosinophiles fairly numerous in pulp. Diagnosis: Chronic splenitis.

Case IV.—C. K., female, aged thirty-eight years, was seen in consultation with Drs. W. Y. Fox and A. R. Crandell, of Taunton. Her illness began abruptly with severe hemorrhage from the stomach in April, 1917. Milder hemoptysis occurred a month later, and again about January 1, 1918. Ascites was first noticed, after parturition, in September 1917, and enlargement of the spleen in February, 1918, after tapping. When seen a week later, the abdomen had partly refilled with fluid, but the spleen could still be felt. It filled the left half of the abdomen down to the crest of the ilium. The liver was not palpable.

On March 2, 1918, she was transfused and the spleen immediately removed by Dr. Edward Richardson. The liver was felt to be considerably enlarged and finely irregular. Improvement was prompt and striking, and at the end of a month she resumed her household duties. On April 27, however, she became suddenly ill, with temperature of 104° F. One of her children had scarlet fever, but the patient presented no evidence of this disease. Chills, sweats and fever of a septic type continued and she died in August, above five months after operation. The cause was assumed to be septic endocarditis, although definite demonstration of this condition was lacking.

The blood, eleven days before splenectomy was as follows: Hemoglobin, 43 per cent; red corpuscles, 2,840,000; leukocytes 750; polymorphonuclear neutrophiles, 66 per cent; lymphocytes, 18 per cent; endothelial leukocytes, 16 per cent. Smears showed only slight changes in color, size and shape of the red corpuscles; no erythroblasts; the platelets seemed much decreased.

On July 9, about four months after operation, and ten weeks after the onset of the septic fever the figures were as follows: Hemoglobin, 66 per cent; red corpuscles, 2,552,000; leukocytes, 19,000; polymorphonuclear neutrophiles, 88.5 per cent; lymphocytes, 6.5 per cent; mast cells, 1.5 per cent; platelets about normal.

The spleen was examined by Dr. W. F. Whitney: "It was smooth externally and measured 23 by 15 by 5 cm. On section it was homogeneous, the follicles were indistinct, and of firm consistency. Microscopical examination showed proliferation of the endothelial lining of the blood sinuses, in places forming a low grade of connective tissue. Diagnosis: Chronic hypertrophy."

Case V.—M. J., female, aged forty years. She admitted taking an occasional glass of ale. She had malaria in 1909 and an abdominal operation in 1912, at which time she was told that her spleen was enlarged. After this she had occasional "spells," lasting a few days and characterized by swelling of the abdomen. In August, 1919, she began to lose weight, and to suffer from dyspnea and steadily increasing distension. She came to the City Hospital, October 11, 1919. There was moderate emaciation and pallor, marked ascites, and a spleen which extended slightly below the navel. The liver was not palpable. The hemoglobin was 20 per cent; red corpuscles, 1,664,000; leukocytes, 1490; polymorphonuclear neutrophiles, 85 per cent; lymphocytes, 8 per cent, large mononuclears, 7 per cent; no nucleated red corpuscles; moderate achromia; platelets probably somewhat decreased.

The abdomen was tapped twice, a total of 15½ quarts of clear fluid being removed. On October 30, Dr. A. R. Kimpton transfused 900 cc of blood. This was followed by a rise of hemoglobin to 45 per cent and by much clinical improvement. Splenectomy was done, November 4, by Dr. Kimpton. At operation a hard, hobnailed liver was felt. She left the table in severe shock and died the next morning. This is the only operative death in the series.

The spleen weighed 7000 gm. Microscopically it showed congestion and fibrosis as in the others of this group.

Case VI.—M. W., female, aged fifty-six years. Patient of Dr. E. T. Manix, of Lynn. There was nothing in the history or physical state to suggest alcoholism or syphilis. She gave a history of "indigestion" for thirty-nine years, with repeated hematemesis. When seen by the writer in September, 1919, pallor, weakness and dyspnea had been progressive for seven years. She was moderately emaciated and pale. The liver edge could be felt only on deep inspiration. The spleen extended 4 cm. below the costal margin. By January, 1920, the spleen had increased to 10 cm., the liver was no longer palpable, and there was slight ascites. Roentgen-ray showed gall stones and an hour-glass stomach, with what appeared to be an active ulcer. The Wassermann test was negative.

Two transfusions resulted in much improvement. Splenectomy was done, February 10, 1920, by Dr. A. R. Kimpton. There was some ascites and the presence of gall stones and an hour-glass stomach was verified, though neither of these lesions was operated upon.

CASE VI.—SPLENECTOMY FOR BANTI'S DISEASE, FEBRUARY 10, 1920.

Date.	Hemolobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.						Nucleated red corpuscles.	Reticulocytes per cent	Platelets.	Remarks.
				Polymorphonuclear neutrophiles.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.	Myelocytes.				
Sept. 5, 1919	33	2,136,000	1,650	67.0	28.0	2.0	2.0	2	1.0	0	7.5	Decreased	
Jan. 14, 1920	24	1,800,000	3,600	72.0	16.0	4.0	8.0	0	0.0	0	0.6	Decreased	
" 27, 1920	41	3,300,000	2,800	60.0	32.0	4.0	4.0	0	0.0	0	2.4	Decreased	Transfused Jan. 23.
Feb. 4, 1920	51	3,900,000	6,000	52.5	35.0	12.5	0.0	0	0.0	0	..	Increased	Transfused Feb. 2.
" 11, 1920	52	4,000,000	8,000	82.5	14.0	2.0	0.5	0	1.0	..	3.6		
" 12, 1920	52	4,300,000	8,000	87.5	3.5	1.5	1.0	0	7.5	Many	5.8		
" 14, 1920	52	3,500,000	10,200	79.0	4.0	5.0	1.0	1	9.0	Few	9.8		
" 20, 1920	56	3,800,000	6,600	77.5	5.0	2.0	1.5	1	13.0	..	5.2		
Mar. 2, 1920	60	4,600,000	7,000	40.0	40.0	12.0	0.0	8	....	..	3.4		
" 9, 1920	62	4,300,000	7,000	40.0	39.0	10.0	8.0	2	....	..	5.7		
Apr. 3, 1920	50	2,300,000	5,000	55.0	24.0	15.0	1.0	5	0.5	..	....	600,000	Hemorrhoids, bleeding.
May. 4, 1920	76	3,750,000	5,600	50.0	34.5	13.0	0.5	2	....	0	1.1	Abundant	
Nov. 10, 1920	88	3,360,000	5,400	41.0	46.0	11.0	0.0	1	1.0	..	0.9	596,000	
Apr. 10, 1923	73	3,184,000	8,850	50.5	33.0	12.5	2.0	1	1.0	0	....	248,000	Recent hemorrhage.

The clinical results were excellent. The anemia improved, but did not wholly clear up—which is not remarkable when it is remembered that an active gastric ulcer was left undisturbed and that she continued to bleed from hemorrhoids. The need for further operative work was recognized, but she refused, perhaps wisely, to see the matter in this light.

The spleen weighed 510 gm. Dr. Mallory reported: "Congestion and fibrosis; no thromobosis of portal or splenic vein."

Recently (April, 1923), she has had for the first time since operation a slight hemorrhage from the stomach. After a couple of days in bed, she got up and went about her daily housework as usual. She now considers herself perfectly well, as there is nothing the matter with her except cirrhosis of the liver, gall stones, gastric ulcer, hemorrhoids and a considerable degree of vascular hypertension.

Cases II to VI obviously belong in the clinical group characterized by a large fibrotic spleen, the secondary type of anemia with leukopenia, tendency to hemorrhage from the stomach and ascites in the later stages, and susceptibility to marked improvement after splenectomy. Of course they do not all show all of these symptoms, Case II in particular representing an early stage. Most clinicians will classify such cases either as splenic anemia or as Banti's disease, although in the present state of knowledge it is safer to classify them by definition rather than by name. Writers have differed in their use of the term "Banti's disease," especially as regards the significance of the changes in the splenic and portal veins. Apparently Banti himself, in his long series of papers expressed different views at different times. As regards what to include under the term splenic anemia, the writer is in accord with the characteristically vigorous words of W. J. Mayo,[3] who says that, inasmuch as cases are taken out of this category as soon as the etiology is known, "incomplete knowledge is essential to the diagnosis. . . . I believe we would get a better idea of splenic anemia if we made the pathological condition of the spleen and its effect on the blood the criterion, and classified as splenic anemia all cases of known causation as well as those of unknown causation."

The most significant question here concerns the relationship of such cases as these with cirrhosis of the liver. That such association does exist, at least in the later stages, is of course well known. Banti and most of the earlier writers on this subject considered the changes in the liver to be secondary to those in the spleen.[1 4] Of late the question as to whether the changes in the liver or vessels may not be the primary factor is becoming more insistent.

The spleens of the cases herewith reported show nothing that could not be explained by long continued chronic passive congestion. Dr. F. B. Mallory, who examined most of them, states that the changes are precisely those that occur in ordinary cases of alcoholic cirrhosis. Not one of these patients gave a history of alcoholism

and surely four women and one young boy hardly constitute a group in which one would expect chronic alcoholism to be the common etiological factor. Yet at operation three showed livers which seemed cirrhotic. One had a spleen so greatly ptosed that its position might have been the cause of chronic congestion. The remaining case showed a normal liver at autopsy. As he lived several months after splenectomy, the condition of the splenic vessels can not be stated. It should be said that chronic passive congestion of the spleen does not necessarily imply cirrhosis of the liver though that is perhaps the commonest cause—sclerosis or thrombosis of the splenic or portal vein above the junction, or marked ptosis of the spleen, would give the same conditions—at least in a mechanical sense.

Whatever may be the solution of this problem, the important clinical fact is that these big, fibrotic spleens, however brought about, are, at least potentially, causes of anemia and after their removal the anemia promptly clears up. Further, the ascites and hemorrhages occurring in the later stages may be greatly improved and often made to disappear by the same operation. It will greatly clear the air if clinicians will bear these facts in mind, and not be too fussy about the primary cause of the splenomegaly.

Two Cases of Alcoholic Cirrhosis. CASE VII.—J. F., male, aged twenty-five years, was referred to me by Dr. H. P. Towle. This man was a steady drinker, who had, when he came under observation, suffered for but two weeks from dyspnea, edema and ascites. He was pale and delicate-looking, with the velvety skin characteristic of the confirmed alcoholic. He had mild psoriasis. The abdomen was greatly distended with fluid and there was much hard, brawny edema of the legs. The liver could not be felt. The spleen was 5 cm. below the ribs. The urine contained a slightest possible trace of albumin, but no casts.

After being tapped twice at intervals of a week, splenectomy was performed by Dr. H. B. Loder. At operation the liver was felt to be hard and "hobnailed." He was followed for ten weeks after operation, during which period there was little if any ascites and no edema. Perhaps, because he felt the need of a less arid climate, he then went to Ireland, where he became involved in the prevailing political disorders and was repeatedly arrested. He returned to Boston and reported for examination twenty-one months after the splenectomy, feeling perfectly well and still free from edema and ascites. The urine contained a large trace of albumin, hyaline and granular casts and blood cells. These soon disappeared under treatment, but when last seen, he had slight glycosuria. The psoriasis cleared up shortly after operation and recurred for only one short period nearly two years later.

The spleen weighed 690 gm. Dr. Mallory reported: "Marked fibrosis and moderate congestion."

CASE VII.—SPLENECTOMY FOR CIRRHOSIS OF THE LIVER, JUNE 18, 1920.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.						Normoblasts.	Megaloblasts.	Reticulocytes, per cent.	Miscellaneous.
				Polymorphonuclear neutrophiles.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.	Myelocytes.				
May 26, 1920	100	4,000,000	2,800	64.5	25.5	7.5	1.5	1.0	0.0	0	0	1.6	Coagulation factors normal.
June 18, 1920	95	4,500,000	2,200	66.0	18.5	5.0	10.0	0.5	0.0	0	0	2.1	Before splenectomy.
" 18, 1920	92	4,800,000	5,000	59.0	28.0	3.0	10.0	0.0	0.0	2	4	...	After splenectomy.
" 19, 1920	92	3,800,000	14,000	81.0	6.5	9.0	0.0	0.0	3.5	0	0	3.0	Platelets diminished
" 21, 1920	62		17,000	82.5	9.5	7.5	0.5	0.0	0.0	0	0	6.2	Platelets increased.
" 26, 1920	80	3,870,000	20,800	85.0	2.5	9.5	1.5	0.0	1.5	0	0	...	Platelets, 800,000.
" 30, 1920	97	4,100,000	20,200	82.5	5.5	3.5	1.0	0.0	7.5	0	0	6.8	Platelets, 278,000.
July 6, 1920	102	4,200,000	7,600	77.5	11.0	1.0	1.5	1.5	7.5	0	0	9.5	
" 13, 1920	127	4,900,000	20,400	74.5	9.0	9.5	2.5	0.0	4.5	0	0	2.8	Platelets normal.
Aug. 6, 1920	74	3,930,000	8,500	48.0	36.0	6.0	4.0	2.0	4.0	0	0	1.3	
Apr. 1, 1922	84	4,056,000	11,000	64.0	20.5	12.5	2.0	1.0	0.0	0	0	...	Platelets, 152,000.

CASE VIII.—D. B., aged fifty years, an Italian laborer, who used wine freely. He came to the Boston City Hospital for hernia. During the routine examination, the liver and spleen were both found to extend 5 cm. below the costal margin. There was slight jaundice, but no ascites. The Wassermann reaction was negative. He refused operation for the hernia and was discharged. About three months later he was readmitted with marked ascites, jaundice and edema of the legs.

Splenectomy was done by Dr. J. C. Hubbard. At operation both spleen and liver were aherent to adjacent structures. The liver was not noticeably enlarged; adhesions prevented satisfactory palpation.

The results were disappointing as compared with the preceding case. There was some improvement in his general condition and the anemia disappeared, but he continued to need tapping about once a month. He was lost sight of after four months.

The spleen was the size of two fists. Dr. Mallory's report was, "Increase of stroma; chronic fibrosis."

CASE VIII.—SPLENECTOMY FOR CIRRHOSIS OF LIVER AND SPLENOMEGALY, AUGUST 18, 1921.

Date.	Hemoglobin, per cent.	Red corpuscles.	Leukocytes.	Differential count in percentages.					Platelets.
				Polymorphonuclear neutrophiles.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.	
Aug. 1, 1921	70	3,180,000	4,000	70.0	29.0	1	0	0	
" 22, 1921	75	2,280,000	14,000	91.0	6.0	3	0	0	Decreased.
Oct. 5, 1921	96	4,500,000	12,600	53.5	27.5	18	1	0	166,000

These two cases are classed as cirrhosis of the liver chiefly because they were alcoholics. So far as the structural changes in the spleens are concerned, they might equally well have been classed in the preceding group, and Case VIII, as he had the characteristic anemia which cleared up after splenectomy, should perhaps have been so classed. The truth is that cirrhotic splenomegaly and splenomegalic cirrhosis are so closely allied that a distinction is impossible, clinically or pathologically, and it seems quite pointless to make the existence of changes in the splenic or portal vein the criterion.

Mayo[5] has reported 11 splenectomies for portal cirrhosis, with 4 deaths—not a very high mortality when it is considered that all 11 were advanced cases with ascites and hemorrhages from the

stomach. Any internist who has handled such cases knows how hopeless they are under medical treatment. Four of Mayo's cases were greatly benefited, 1 being alive five years after operation.

The beneficial effects of splenectomy in cirrhosis have been attributed partly to cutting off the supply of toxic material presumably elaborated in the spleen and passed on to the liver, and partly to mechanical relief of the portal circulation. The existence of any such toxic material is wholly hypothetical, but there can be no doubt of the mechanical relief. The blood supply of the spleen is very large and it is said that normally 25 to 30 per cent of the portal blood comes from the splenic vein. Presumably in these enormously enlarged spleens the proportion is much higher. The relief to the narrowed portal channels from the cutting off of this large amount of blood is probably enough to account for the effect of the operation on ascites and hemorrhages. Splenectomy alone was done in both cases here reported. Mayo combines splenectomy with omentopexy.

Hemolytic Jaundice. CASE IX.—J. S., male, aged twenty-seven years. His illness began in the fall of 1919 with acute pain in the left side followed by jaundice, which, he thought, had not cleared up. He complained only of drowsiness and debility. When seen, March 26, 1920, there was but slight pallor, the complexion being a muddy yellow—he was not definitely jaundiced. The liver was slightly enlarged and the hard edge of the spleen was felt at the level of the umbilicus. There was no history of alcoholism, and the Wassermann reaction was negative. The blood findings including fragility tests and reticulated red counts are shown in the chart.

Splenectomy was done by Dr. F. J. Cotton on May 28, 1920. There were no adhesions, no ascites and no definite enlargement of the liver. The patient, who had, it is true, not been very ill or wholly incapacitated, expressed himself as being greatly improved. When last seen (September, 1921) his condition remained normal.

The spleen weighed 865 gm. Dr. Mallory reported only congestion and fibrosis.

This is obviously the acquired (Hayem-Widal) type of hemolytic jaundice, the distinguishing features being the marked fragility of the red corpuscles, and the large percentage of reticulated red corpuscles previous to the disappearance of the anemia after operation. The acquired type, unsplenectomized, is universally admitted to be less favorable in prognosis than the congenital, and therefore to a greater extent an indication for splenectomy. This patient was told that he might live for years without splenectomy, but that operation, if successful, would relieve his symptoms. He elected to take the risk. It seems to the writer that the question should always be put up to the patient in some such way. This subject has been thoroughly covered in the recent monograph of Tileston,[6] and further comment seems unnecessary.

CASE IX.—SPLENECTOMY FOR HEMOLYTIC JAUNDICE, MAY 28, 1920.

Date.	Hemoglobin, per cent.	Red corpuscles.	Leukocytes.	Differential count in percentages.						Normoblasts.	Hemolysis in hypotonic NaCl solution in percentages.		Reticulocytes, per cent.	Miscellaneous.
				Polymorphonuclear neutrophiles.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.	Myelocytes.		Begins.	Ends.		
Apr. 1, 1920	61	3,500,000	8,200	80.0	14.0	4.0	1.0	1.0	0.0	0	0.575	0.450	16.0	Coagulation factors normal; serum urobilin +.
May 14, 1920	89	3,200,000	5,000	53.5	32.0	13.5	0.5	0.0	0.5	0	...	...	11.7	Platelets, 300,000.
" 28, 1920	65	...	9,400	39.2	58.4	1.7	0.4	0.0	0.0	0	0.600	0.400	14.5	Blood from splenic artery.
" 28, 1920	75	3,500,000	18,800	30.5	58.0	11.0	1.5	0.0	0.0	0	0.600	0.425	7.2	Blood from splenic vein.
" 29, 1920	72	5,500,000	17,200	91.0	6.0	3.0	0.0	0.0	0.0	0	...	...	13.4	
June 2, 1920	95	5,700,000	5,200	48.0	33.0	16.0	3.5	0.5	0.0	0	...	...	3.8	Platelets appear increased.
" 4, 1920	95	4,900,000	8,400	57.5	26.5	9.5	2.0	0.0	4.5	1	0.550	0.450	2.1	Platelets appear decreased.
" 15, 1920	89	5,300,000	6,000	34.8	45.6	11.3	3.5	1.0	3.5	1	0.500	0.350	1.0	Platelets appear increased.
" 30, 1920	117	5,400,000	10,400	42.5	44.5	11.5	0.0	0.0	1.5	0	0.500	0.300	2.3	Platelets appear increased.
Aug. 12, 1920	110	5,430,000	8,700	32.5	53.0	8.5	3.0	2.0	0.0	0	0.475	0.350	0.6	Platelets appear increased.
Sept. 24, 1920	111	6,880,000	19,400	..	..	..	..	..	..	..	...	...	...	Platelets, 438,000.
Sept. 9, 1921	70	6,400,000	12,000	..	..	..	..	..	..	..	...	...	...	Smears normal.

Hypoplastic Anemia. CASE X.—O. S., male, aged thirty years. This was an unusual case of "chronic aplastic anemia," or "hypoplastic anemia," which will be reported in detail later. The condition is known to have existed since 1915, for an examination of the blood by Dr. A. A. Hornor at that time showed anemia of the peculiar type so evident later. He had several attacks of jaundice and hemorrhages into the skin, from the nose, from tooth extraction and particularly into the vitreous of the right eye, the latter having recurred frequently for six years.

He was referred to the writer by Dr. E. W. Clap in February, 1920. He was pale, with a peculiar yellowish, "sour-dough" tinge. The vitreous of the right eye was opaque and there was a retinal hemorrhage on the left. On the shins there were purpuric spots and some old, brown, pigmented areas. Neither liver, spleen nor lymph nodes were palpable. No relief resulted from any of the various therapeutic measures tried, except from transfusion. In all he received eighteen transfusions, aggregating about 10,000 cc of blood. Each caused general improvement and temporary cessation of hemorrhage, but after a few days or weeks the anemia and the bleeding would recur with inceasing intensity till he was again transfused.

Splenectomy was undertaken as a last resort in the hope of bringing about increased resistance of th red cells as well as increased activity of the marrow. After four preliminary transfusions, Dr. Kimpton removed the spleen on July 1, 1921. There was no bleeding and convalescence was uneventful.

The results, so far as retarding the advance of the anemia is concerned, were disappointing. Inspection of the accompanying table will show, however, that the figures for platelets ran distinctly higher than before, and it is notable that there were no further hemorrhages—about the only practical benefit which the patient derived from the operation. He died in February, 1922. There was no autopsy.

The spleen was slate gray, measured 11 x 8 x 5 cm., was of rather firm, rubber-like consistency, and the cut section was dark red. Microscopically it showed chronic splenitis.

Hodgkin's Disease. CASE XI.—N. W., female, aged sixty-five years, was referred by her family physician to Dr. J. L. Ames, through whose kindness I saw her after operation and am permitted to include her case in this series. In December, 1920, she had some minor digestive symptoms and rapidly lost strength and color. A month later the enlarged spleen was noticed. It increased rapidly until it extended inward to the median line and downward below the umbilicus. There was a tumor, apparently an enlarged lymph node, about the size of a walnut, under the angle of the jaw on the right, and some smaller nodes in the neck. There was no jaundice

CASE X.—SPLENECTOMY FOR HYPOPLASTIC ANEMIA, JULY 1, 1921.

Date.	Hemoglobin, per cent.	Red corpuscles.	White corpuscles.	Differential count in percentages.						Normoblasts.	Megaloblasts.	Reticulocytes per cent	Platelets.	Miscellaneous.
				Polymorphonuclear neutrophiles.	Lymphocytes.	Large mononuclears and transitionals.	Eosinophiles.	Mast cells.	Myelocytes.					
Oct. 29, 1915	..	2,400,000	2250	28.0	58	14	0	0	0.0	0	0			
Feb. 4, 1920	29	1,600,000	4600	53.5	44	2	0	0	0.5	0	0	...	Very rare	Coagulation-time, 14 min.; bleeding-time, 27 min.
Mar. 4, 1920	71	3,900,000	3400	48.0	48	4	0	0	0.0	0	0	6.2	...	After four transfusions, total 2400 cc.
Aug. 8, 1920	26	1,270,000	3200	40.0	57	3	0	1	0.0	0	0	4.6		
Oct. 4, 1920	26	1,100,000	1600	40.0	50	9	0	1	1.0	0	0	4.7	60,000	
May 17, 1921	25	1,034,000	1400	47.0	40	11	0	1	1.0	0	0	1.4	Rare	Transfused, May 8, 1921.
" 21, 1921	22	958,000	1000	..	..	..	..	..	..	..	..	3.2	16,000	
June 13, 1921	21	960,000	....	..	..	..	..	..	..	..	..	...	20,000	Transfused 600 cc, May 23.
July 1, 1921	67	2,510,000	3000	..	..	..	..	..	..	..	..	...	64,000	After 4 transfusions in two weeks; total, 2400 cc.
" 7, 1921	45	1,760,000	2200	63.0	32	2	0	0	1.0	0	0			
" 20, 1921	35	1,345,000	5000	..	..	..	..	..	..	..	..	...	140,000	
Aug. 1, 1921	32	1,300,000	2700	..	..	..	..	..	..	..	..	...	96,000	
Nov. 16, 1921	30	600,000	2600	43.0	47	7	1	0	2.0	1	1	7.0	188,000	Transfused, Oct. 8.
Dec. 5, 1921	47	1,800,000	2000	..	..	..	..	..	..	..	..	2.8	60,000	Transfused, Nov. 10 and 25.

and no ascites. Her general condition was very unfavorable and she seemed unlikely to live more than a few weeks.

Splenectomy was successfully done by Dr. F. G. Balch, January 14, 1921. The gland in the neck was afterward treated by the Roentgen-ray without effect and is still about its original size. Now, over two years after operation, the patient considers herself perfectly well.

The blood, just before operation was as follows: Hemoglobin, 60 per cent; red corpuscles, 2,700,000; leukocytes, 5000; platelets, as seen in smears, apparently decreased. On February 3, 1921, three weeks after the operation, the blood was examined by the writer with the following results: Hemoglobin, 56 per cent; red corpuscles, 2,760,000; leukocytes, 16,000; platelets, 380,000; volume index,[7] 1.27; polymorphonuclear neutrophiles, 93.5 per cent; lymphocytes, 3.5 per cent; large mononuclears and transitionals, 1.5 per cent; mast cells, 0.5 per cent; myelocytes, 1 per cent; rare normoblasts; reticulocytes 1.5 per cent. On April 20, 1923: Hemoglobin, 87 per cent; red corpuscles, 4,616,000; leukocytes, 7400; platelets, 336,000; polymorphonuclear neutrophiles, 63 per cent; lymphocytes, 30 per cent; large mononuclears and transitionals, 5 per cent; eosinophiles, 2 per cent; reticulocytes, 0.2 per cent.

The spleen was about 10 inches long. It presented a number of opaque nodules which proved to be infarcts. Microscopically it showed large, confluent masses of lymphoblastic tissue, with mitotic figures. Dr. J. Homer Wright's diagnosis was Hodgkin's disease.

This case is probably to be classed as Hodgkin's disease, that is, lymphoblastoma without massive invasion of the blood by newly formed lymphocytes. However, in the absence of the usual clinical feature of widespread involvement of lymph nodes, and particularly in view of the widely different views of pathologists as to what constitutes this disease, it is perhaps best not to be certain. The usual method of handling such a case would doubtless be to begin by excising the gland in the neck for histological examination. Had this been done and had the examining pathologist reported Hodgkin's disease or lymphoblastoma, it is improbable that splenectomy would have been performed. This patient refused to have the gland removed, as a previous attempt to do so had resulted in a bothersome hemorrhage. This and the favorable outcome disarms criticism, and even if relapse should occur now, over two years after operation, the procedure has justified itself. It is possible that this case was one of the rare instances of primary Hodgkin's disease of the spleen, and that the hypertrophy of the cervical glands was an independent lesion. If cases of Hodgkin's disease confined solely to the spleen occur, it would probably be impossible to differentiate them from splenic anemia until the spleen is removed and

examined. The case here reported justifies splenectomy in such conditions.

GENERAL COMMENT. *The Blood.* No comment is necessary on the blood conditions previous to operation, since these cases showed nothing different from the findings well known to exist in the diseases concerned. In certain ways, however, the effects of splenectomy on the blood pictures differed from the generally accepted facts.

After experimental splenectomy in normal dogs, Pearce, Krumbhaar and Frazier[1] observed secondary anemia which increased for about six weeks, and gradually disappeared in three months or more. Wolferth[8] found similar changes in rats and Hitzroth[2] the same in 4 human cases splenectomized for trauma, as well as in several patients where diseased spleens were removed.

Unfortunately there was no examination of the blood in the only normal spleen in my series until the seventeenth day, at which time the figures showed evidence of an unusually rapid recovery from the severe loss of blood from the ruptured organ. By the end of a month there was slight polycythemia, which persisted for at least two years. Only one of the splenectomies for disease (Case VII) was followed by definite increase of anemia, and in this case it lasted but twelve days. Of the five previously anemic cases in which adequate studies of the blood were made both before and after operation, only one, the hypoplastic anemia (Case X), failed to show prompt improvement in the anemia. One (III) was normal in two to four weeks, one (VIII) in six weeks, and one (IX) in five days. In the remaining case (VI) the effects of splenectomy were masked by the facts that several transfusions had been done previous to splenectomy and that her hemorrhoids continued to bleed for several weeks afterward, but the beneficial effects were shown by the persistence of the artificially high figures existing as a result of transfusion before operation and by the gradual establishment of a normal blood in the months following.

On the whole the improvement as regards the anemia was more striking than these figures would indicate. In cases IV and XI, both seen in consultation, improvement was so obvious that the physicians in charge considered further study of the blood superfluous—which is gratifying enough, but not improving to the statistics!

The resistance of the red corpuscles to hemolysis in hypotonic salt solutions showed an increase after splenectomy in the few cases where it was studied—which is in accordance with the results of others. The case of hemolytic jaundice (IX), where resistance was low before operation, showed some increase after splenectomy, but the figures did not reach normal. It is interesting to note that in the normal case (I) the resistance remained abnormally high at the end of thirteen years.

Most of these cases showed a few nucleated red cells, usually

normoblasts, shortly after splenectomy. Only rarely were Howell-Jolly bodies seen. No case had any definite "blood-crisis." Neither was there any consistent effect on the proportion of reticulocytes.

In accord with the results of others, all of our cases (except the one with hypoplasia) showed leukocytosis after splenectomy. The degree of leukocytosis and the time the maximum figure was reached were so variable as to defy analysis, but in all but two or three the maximum was definitely above normal. In all but three the leukocytosis persisted as long as the cases were observed.

Analysis of the cell-types concerned in these leukocytoses is necessarily rather vague, since in normal individuals the different types undergo wide fluctuations and definite standards do not exist. In the first few days after operation the increase seemed due to polymorphonuclear neutrophiles. Later, in the persistent stages, the lymphocytes and endothelial leukocytes (large mononuclears and transitionals) were also increased. Eosinophilia was present to a slight degree in most of the cases at variable periods after operation. Only in Case II was it marked and persistent—the highest figure being 25 per cent (2628 per c.mm.). It is often more apparent if absolute figures are used rather than percentages.

The platelets showed a decided tendency to increase in number after splenectomy. This is in accordance with the recent work of Brill and Rosenthal,[10] who have advocated splenectomy for the relief of the thrombopenia of purpura hemorrhagica. While the figures are too incomplete to allow inferences as to the duration of this change, it may safely be said that it outlasted the period of recovery from operation and is therefore to be classed along with the increase of red corpuscles and leukocytes as a result of splenectomy *per se*. Case X is particularly interesting in this respect. Apparently his marrow was so damaged that it was unable to respond to splenectomy either by increased formation of red cells, or leukocytosis, but the platelet-forming function was still able to respond, though not in a normal degree.

Why does removal of the spleen lead to such prompt recovery from anemia? The answer might conceivably be that the abnormally active processes of blood destruction consequent upon the splenic disease are brought to a standstill by its removal. That splenectomy does, in fact, result in decreased elimination of pigment derived from hemoglobin may be accepted, and probably the beneficial effects of the operation are partly due to lessened blood destruction.

On the other hand the appearance in the blood of nucleated red corpuscles, the increase of leukocytes, including those types originating in the marrow, and of the platelets as well, would seem to indicate a speeding up of the process of blood-formation. Hyperplastic changes in the marrow after splenectomy have been

shown by various investigators.[1] It may be taken as a fact, then, that, while there is increased resistance to hemolysis of the red cells and decreased cell-destruction, there is also a marked increase in the activity of the blood-forming tissues consequent upon the loss of the spleen.

Fatalities. Four of the 11 cases here reported are known to be dead. One was an operative death and calls for no comment. Another was the case of hypoplastic anemia, in which splenectomy if it did not materially retard the downward course of the disease, certainly did not hasten it. Of the two remaining fatal cases, both splenic anemias, one (III) died four and a half months after operation, of acute appendicitis, the other (IV) in five months of an infection of unknown cause. Although these conditions would hardly seem to have any etiological connection with splenectomy, the cases are interesting in view of a considerable amount of experimental investigation on the influence of splenectomy on resistance to infection. Morris and Bullock[9] summarized the literature in 1919. Their own extensive and carefully controlled work leaves no doubt that splenectomy greatly increases the susceptibility of rats to rat plague. The writer knows of no published evidence that similar increased susceptibility occurs in man. However, it would certainly seem wise to bear in mind the possibility of its occurrence, when considering the advisability of operation.

The Indications for Splenectomy. Splenectomy is indicated in most cases of clinical splenic anemia, without much regard to what causes the splenic enlargement. As many of the unoperated cases get along in comfort for years, it is reasonably safe to postpone operation until the anemia becomes incapacitating. Even after ascites and gastric hemorrhages have begun, operation will often result in clinical cure. In hemolytic jaundice it is generally indicated in the acquired and sometimes in the congenital cases and promises complete relief.

In alcoholic and other cirrhoses of the liver, it is indicated only in selected cases—mostly those in advanced stages with ascites. As the effects of splenectomy are probably for the most part purely mechanical, best results will be obtained where the spleen is unusually large and relief to the portal circulation is correspondingly great. If such patients also have anemia and leukopenia, they are clinically indistinguishable from, if not pathologically identical with, Banti's disease and splenectomy is by all means indicated.

Of several forms of splenic anemia not illustrated in my series, it may be said that in Gaucher's disease, splenectomy should generally be done, and that in von Jaksch's disease it is sometimes necessary. Evidence is accumulating to show that the enlarged spleens sometimes seen in syphilis, malaria and other chronic infections are not *per se* innocuous and their removal has in certain reported cases been followed by marked improvement.[3 5]

It is generally admitted that splenectomy is contraindicated in leukemia, with which conclusion the writer emphatically agrees. Few cases have survived the operation, and even where skilled surgery has procured a successful operative result, there has been little or no gain to the patient.

Primary polycythemia is another condition frequently associated with splenomegaly in which splenectomy is contraindicated,[1] both on theoretical and clinical grounds. The question of splenectomy in pernicious anemia is still perhaps a moot point. It may be safely said that, while the operation has a place in the treatment of this disease, its value is limited, and the results obtained are in no way comparable with those seen in such diseases as splenic anemia and hemolytic jaundice.

One final caution: Splenectomy ought never to be decided upon hastily and without careful study of the case. A delay of several months is generally advisable. Otherwise, one may find out too late that he has mistaken leukemia in an aleukemic stage for Banti's disease, or polycythemia for hemolytic jaundice. Even if the patient is quite sick and in a stage of advanced anemia, a transfusion or two and a few abdominal taps will tide him along and perhaps, as in Case VI, lead to a degree of temporary improvement that will greatly increase the chance of success, besides giving opportunity for study. Reasonable delay will rarely injure the patient's chances and time is a great diagnostician.

NOTE.—Since this paper was presented for publication we have had three more splenectomies. The first was a case of chronic purpura hemorrhagica, in which complete relief has now lasted four months. The second was a case of pernicious anemia, the result of operation being a prolonged remission, but accompanied by little subjective improvement. The third was a remarkable case of anemia following pregnancy, which promptly recovered after splenectomy, repeated transfusions having failed.

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STUDIES IN CHOLELITHIASIS.

IV. The Late and Permanent Results of the Various Types of Operation on the Biliary Passages with Especial Reference to the Cholesterol Metabolism.

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In previous studies[1] on cholelithiasis it was shown that knowledge of the actual anatomical conditions was necessary for a proper conception of the underlying pathological disturbance initiating disease of the bile passages with stone formation. Then it was possible to distinguish that the cases fell into a number of groups in one of which (1) the dominant factor was a disturbance of the cholesterol metabolism. (The other groups included (2) the purely infectious cases and (3) that in which infection and disturbed metabolism were intimately bound together.)

An investigation of the effect that the various types of operation[2] upon the biliary passages had upon these conditions, especially the effect upon the underlying metabolic disturbance when the latter was present, showed that in a certain number of the patients the immediate effect of the operation differed from the one ultimately to be observed if the cases were followed over long periods of time. These immediate effects can be summarized as follows:

A. The operation of cholecystectomy accomplishes two objects: (1) It removes the local focus of infection, when that is present; (2) it removes the reservoir of bile with its contained stones and stagnant bile, thereby also removing some of the end results of the pathological disturbance in the cholesterol metabolism which has already taken place: The former removes an agent which has complicated this biological disturbance or which has initiated the stone formation. The only permanent effect accomplished is the removal of the infectious process whenever that is present. The effect upon the cholesterol metabolism is nil. With this operation efficient bile drainage is only possible through a choledochotomy opening.

[1] We are indebted to Drs. Lilienthal, Beer, Berg, Elsberg and Moschcowitz, chiefs of the surgical services of Mount Sinai Hospital, for their coöperation in these studies.

[2] These types include: (1) Cholecystectomy with or without drainage of the cystic or hepatic ducts and with or without choledochotomy and drainage of the common duct; and (2) cholecystostomy with or without choledochotomy and drainage of the common duct.

B. The operation of cholecystostomy accomplishes the following objects: (1) It enables one to remove the end-products of disturbed cholesterol metabolism somewhat better than a cholecystectomy without bile drainage. (2) It affords a surgical method, inferior to cholecystectomy, for draining the infected area: this does not guarantee that the source of infection has been removed and healing may take place before this source has completely disappeared; recrudescences of infection may, therefore, be expected and do actually occur. (3) It affords a method of biliary drainage.

The effects of the chief means of operative bile drainage[3]—drainage into the gall-bladder and drainage into the common and hepatic ducts—may be summarized as follows: (1) With common duct drainage the system is rapidly depleted of its cholesterol bodies. (2) Gall-bladder drainage does not accomplish this extreme effect unless there be a concomitant obstruction in the common bile duct. (3) The rate of drop of the cholesterol in the blood serum varies and depends upon the initial figure and the length of time of drainage; after a certain minimum is reached, there is no further fall in the cholesterol content of the blood. (4) These effects are obtainable only when the operation has been so performed that proper bile drainage is accomplished and all obstructions have been removed from the ducts. (5) When obstruction is present before operation the complete removal of this obstruction is followed by a fall from the preoperative hypercholesterolemia, the figures reaching a normal level very promptly. (6) If the preoperative figure has been low because of an associated high temperature the drop of temperature following operation is accompanied by a rise in the cholesterol content of the blood to the normal level. (7) When the postoperative drop has been large and there had been no antecedent obstruction the fall is partly due to a lipoid-free diet.

The effect of bile drainage *per se* upon the underlying metabolic activities whose function is the control of the cholesterol content of the body and blood, is probably nil. What is accomplished is the removal of that portion of the cholesterol which exceeds the normal minimum content. How thoroughly this is accomplished depends upon the severity of the metabolic disturbance and especially upon the completeness or incompleteness of the biliary fistula; and when this is complete, one may see the cholesterol content of the blood fall to values below the usual normal.

It is evident from these facts that a choice of the proper operation, efficiently carried out, combined with the intelligent use of bile drainage, restores the cholesterol content of the blood and bile to the normal. It is evident, too, that the essential cause of the hypercholesterolemia has, probably, not been influenced in any way.

In the present communication the more permanent results of

[3] Drainage into the stump of the cystic duct is not efficient.

operation for cholelithiasis are considered. The purpose is the isolation and description of that group of cases with recurrent symptoms in which the dominant element causing the disturbance is some fault in the cholesterol metabolism. At the same time the behavior of the cholesterol metabolism in all of the other cases will also be considered. All of the cases have been grouped as follows:

GROUP I (74 per cent). Cured cases:

1. Infective cases.
2. Cases with slight metabolic disturbance.

GROUP II (26 per cent). Cases with postoperative symptoms:

1. Cases with surgical causes.
   - (*a*) Old cholecystostomy cases.
   - (*b*) Cases with strictured ducts.
   - (*c*) Cases with new and recurrent infections, or persistence of old infection.
2. Stone cases:
   - (*a*) Infective cases—cholangitis.
   - (*b*) Diathetic cases.
3. Diathetic cases:
   - (*a*) Milk cases—easily relievable by diet and not readily recurrent.
   - (*b*) Severe cases.
     - (*a'*) Diet constantly necessary.
     - (*b'*) With attacks of pain and jaundice.
4. Recurrent pregnancy cases.[4]

The cases in this series were not selected in any way but were studied *seriatim* as they were consecutively admitted and discharged from the hospital. The original studies were made in the latter part of 1914, in 1915 and in 1916. Since then the cases have been followed and the subsequent clinical facts and laboratory findings form the criteria upon which the conclusions of this communication are based. The methods of studying the cases and the technic of the laboratory (blood) examinations were detailed in a previous paper of this series. The descriptions of the individual groups as noted above follow.

Cured Cases. The cured cases form the great majority of all of the cases studied and make up a total of 74 per cent.[5] It has been possible to distinguish that the cured cases must include: (1) Those initiated by infection; (2) those initiated by disturbances in the cholesterol metabolism; (3) those in which both of these elements have been working together or have consecutively followed one another.

The purely infective cases are the simplest. An infection having taken place the patient was subjected to operation: a perfect recovery was made and the latter has up to the present remained

[4] The discussion of these cases is reserved for a future occasion.

[5] *Vide infra*, under recurrent symptoms, for explanation of percentage.

permanent. No postoperative symptoms are expected unless some mechanical disability or purely surgical emergency (for instance, intestinal obstruction) takes place. A number of the cases in this group were jaundiced at the time of the primary operation and a hypercholesterinemia was present; the character of the anatomical findings at operation and the laboratory indications of the subsequent activity of the cholesterol metabolism give sufficient evidence that jaundice had no relation to the latter and was due entirely to obstruction of the bile passages. The notes of the following cases form excellent illustrations of this type of case:

CASE I.—In a woman, aged twenty-nine years, the first attack of right hypochondriac pain occurred five days after the birth of her first child. Jaundice was present. Operation disclosed a gangrenous gall-bladder and the common duct seemed compressed from the inflammatory infiltration. A cholecystectomy was done and common duct drainage was instituted. Prior to operation the cholesterol content of the blood was 250 mg. per 100 cc. A high figure —275 mg. per 100 cc—was present six days later coincident with an increase in the jaundice and probably due to the increase in the inflammatory infiltration produced by the operative trauma. Thereafter as this subsided and the jaundice disappeared the cholesterol content of the blood fell to 140 mg. per 100 cc. This patient has remained cured.

CASE II.—This patient, aged fifty-five years, had had symptoms for six years with frequent attacks of colic. The last attack was accompanied by jaundice and on the third day of the jaundice she was operated upon. The blood contained 235 mg. cholesterol per 100 cc. Operation showed stones in a shrunken gall-bladder, which, microscopically, showed chronic productive inflammation, the ducts were clear. Cholecystectomy without bile drainage was done. The convalescence was uneventful. On the seventh day the cholesterol content of the blood was normal. Four months later the patient reported herself in perfect health; the blood content of cholesterol was normal. This patient, too, is cured.

This group also includes a number of cases in which the character of the anatomical findings indicate a total absence of infection, and the examination of the concretions show that these contain from 90 to 100 per cent of cholesterol; both of these facts show almost conclusively that prior to the primary operation, at least one period had occurred in which a hypercholesterinemia was present and that the latter had been reduced to the normal by a precipitation of one or more stones. At the time of operation a hypercholesterinemic state was not present as its causative factor was inactive. The course of affairs subsequent to operation has not included any

new hypercholesterinemic crisis—physiological or other—and the patients have remained cured. The following case illustrates:

CASE III.—This woman, aged thirty-three years, married for one and a half years had had symptoms characterized by attacks of abdominal cramps with vomiting. The physical examination was negative and there was no hypercholesterinemia. Operation showed an anatomically normal gall-bladder containing a single stone of a soap-like translucency and composed entirely of cholesterin. The cholesterol content of the blood remained normal after discharge from the hospital and the patient is cured. The initial cause of the hypercholesterinemia in this patient was probably that associated with pregnancy.

In other similar cases a hypercholesterinemia was present at the time of operation. Drainage having been instituted, the excess of blood cholesterol was removed. Case IV shows that in the post-operative course of such patients the blood content of cholesterol can remain normal; this fact distinguishes this group from one subsequently to be described in which a return of the hypercholesterinemia is associated with the appearance of symptoms.

CASE IV.—A married woman, aged twenty-seven years, was operated upon at the subsidence of the third attack of cholecystitis. Prior to operation the blood contained 200 mg. of cholesterol per 100 cc. A cholecystectomy was done and bile drainage was instituted. The changes in the cholesterol metabolism immediately following operation were as follows:

	Blood cholesterol, mg. per cent.	Bile cholesterol.		Choluria.	Stools.
		Cc.	Mg. per cent.		
June 27	..	225	0.158	None	Acholic.
" 28	0.125	..	0.062	None	Acholic.
" 29	..	25	0.425	None	Acholic.
" 30	..	65	0.515	None	
July 1	..	17	?	None	Colored.
" 2	..	0	...	None	Colored.
" 18	0.195				

In March of the following year the woman reported herself to be in good health without symptoms of any kind. The blood contained 0.12 gm. of cholesterol per 100 cc.

The largest proportion of the cured cases are composed of those in which the operative findings and the laboratory examinations indicate that prior to operation the pathological process had included both infection and disturbances of the cholesterol metabolism. Depending on conditions present, a hypercholesterinemia was, or was not present at the time of operation and bile drainage was

either instituted or omitted by the operator. The absence of any symptoms in the further clinical courses of these patients indicates that the line of treatment was the correct one in the individual case and that the tissues and the metabolic activities are restored to the normal. The following cases illustrate:

CASE V.—A woman, aged forty-eight years, had had two attacks of gall-bladder colic in the six months preceding operation. At the time of operation she was not jaundiced, although there was some bile in the urine; the blood contained 0.1925 gm. of cholesterol per 100 cc. A cholecystectomy was done. The gall-bladder showed slight chronic inflammatory changes and the bile contained some gravel. There was some tendency to diarrhea after the patient left the hospital but otherwise she was symptomless; at the end of two months the cholesterol content of the blood was 135 mg. per 100 cc; the cure has remained permanent.

CASE VI.—In a woman, aged fifty-nine years, operation showed a gall-bladder with much productive inflammation in its walls and with much pericholecystitis. Stones were present in the gall-bladder but the ducts were free. Symptoms had been present for one year; jaundice, however, had never been present. Prior to operation the cholesterol content of the blood was 297.5 mg. per 100 cc. A cholecystectomy was done. Seven months after the operation the patient reported herself to be symptom-free and the cholesterol content of the blood was 197.5 mg. per 100 cc.

CASE VII.—In a woman, aged twenty-six years, right hypochondriac pain without jaundice, vomiting or other symptoms had been present for three years. The blood contained 200 mg. cholesterol per 100 cc. A cholecystectomy was done. The gall-bladder was found to be full of stones and its wall showed productive inflammation. Eight months after operation the patient reported that the symptoms were entirely relieved. The cholesterol content of the blood at that time was 136 mg. per 100 cc.

Cases with Postoperative Symptoms. In the series of 115 cases, postoperative symptoms of one kind or another were present in 26 per cent. We include in this group all kinds of cases, those with mild symptoms—which, according to our studies have an important significance—as well as those with the more severe manifestations necessitating secondary operations. In the reports usually found in the literature only those are recognized which must be operated upon again and in one of the latest communications the number of such is put at 8.5 per cent (Deaver). In the series which we have studied the number of reoperation cases corresponds with this figure and forms about 10 per cent of the total.

A number of communications have been published in the last few years by Eisendrath, Deaver, Judd and Harrington, Deaver and Reimann, and Davis which fully describe the cases in which the postoperative symptoms have been sufficient to require secondary operation. The actual indication for the latter, whether fistula, stone, cholangitis or obstructive jaundice, is of a purely mechanical or surgical nature and the condition as such bears very little, and then only indirectly, on the disturbances of the cholesterin metabolism, except in those stone cases in which it can be definitely proven that the calculi, which are subsequently found in the ducts, were formed since the primary operation. The purely surgical aspects of these conditions have been very amply discussed by the various men mentioned and the discussion needs no repetition here. Wherein these surgical conditions, especially the repeated or continual reformation of stones subsequent to operation, have relationships with disturbances of the cholesterol metabolism, is a topic that we propose discussing on another occasion.

In 16.5 per cent of the cases in our series (64 per cent of those with postoperative symptoms) the dominant and sole cause for the recurrence of symptoms is an underlying disturbance of the cholesterin metabolism. In other series studied elsewhere, such as those indicated previously—Eisendrath, Deaver, Judd, and others, this subject receives no attention and in the majority the symptoms are dismissed as being too mild for special consideration or as being, perhaps, one of the unavoidable sequelæ of an abdominal exploration and operation; at other times the cause is frequently assumed to be "postoperative adhesions." In the severe cases it is most frequently assumed that the symptoms are due to the retention or reappearance of stones in the biliary ducts.

In all of the cases in this group, whether the symptoms be mild, or whether they be severe, a hypercholesterinemia is constantly found. In about two-thirds of the cases the symptoms are very mild, or only moderately severe and the disorder is fairly easily and sometimes permanently controllable by dietetic means. In the remaining third the symptoms are very severe; a cure is difficult to attain by medical means alone and the treatment must be constantly adhered to; relapses are frequent and severe; and operation is on occasion imperatively demanded.

The essential part of the medical treatment is the adherence to a diet from which substances containing fats and lipoid bodies are excluded. The latter include the ordinary fats and butter, cream and the yolks of eggs, the roe of fish and certain fish which are rich in fat, such as salmon and sturgeon, oils, nuts and certain vegetables and fruits such as the olive. In severe cases the restriction in diet must be fairly extreme: the patient is apt to tire very quickly, to rebel and to demand a more liberal choice of food articles. With the more intelligent group of patients, the benefits which quickly

make their appearance are very satisfying and the discomfort of a restricted diet is more or less willingly tolerated. In the others the patient's discontent with the restricted diet must be relieved by permitting on one day of the week a wider choice; with practically all patients this measure suffices.

In the mild cases the symptoms become prominent more because of their persistence and constant presence than because of their severity. Usually there is a dull pain or ache in the region of the liver, or a sense of vague discomfort, described frequently as a bloated feeling. Occasionally the pain gravitates downward toward the iliac fossa. The bowels show a tendency to be constipated. The symptoms are frequently referred to the stomach. The physical findings show no abnormalities. It is difficult to make out any enlargement of the liver: in many the results of the operation have, because of the presence of massive adhesions, fastened the free edge of the liver down in the neighborhood of the scar and it is not possible to say that the liver edge, which is palpable, indicates displacement or some enlargement. The liver is not tender in the mild cases. There is never any jaundice.

In the mild cases the blood examinations show a moderate hypercholesterinemia. The figures in our cases have varied from about 200 to 300 mg. of cholesterol per 100 cc of blood.

After a thorough cleansing of the intestinal tract and some attention to the diet along the lines previously indicated, the symptoms are quickly relieved. The cholesterol content of the blood returns to its normal variations. The following is an illustrative case:

Case VIII.—In June, 1915, a woman aged forty-eight years, had been operated upon and a very adherent, small and contracted gallbladder had been removed. A good recovery having been made she was discharged from the hospital. In September 1915, the patient returned and stated that her symptoms had not been relieved; at this time her blood contained 205 mg. of cholesterol per 100 cc. The patient was instructed as to her diet. In November 1915—one month later—she reported that she was feeling much better: she was directed to persist in the diet and to return for observation at regular intervals. In March, 1916, the notes read that the pain and other symptoms had been entirely relieved: the blood content of cholesterol was normal at this time—162 mg. cholesterol per 100 cc of blood.

This group includes cases in which both cholecystectomy without biliary drainage was done and those in which efficient biliary drainage was obtained. The previous case was not drained. In the following case biliary drainage had been instituted:

Case IX.—A woman, aged fifty-six years, was operated upon in the first attack of cholecystitis of which a prominent symptom was jaundice. Prior to operation the blood contained 237 mg. of choles-

terol per 100 cc. The findings at operation included an empyema of the gall-bladder, a pericholecystitic abscess, and stones in the common bile duct. Cholecystectomy and choledoschotomy were done and common duct biliary drainage was instituted. The condition of the cholesterol metabolism during the convalescence is shown in the table:

	Blood cholesterol, gm. per cent.	Bile cholesterol.		Choluria.	Stools.
		Cc.	Mg. per cent.		
June 25	..	270	0.140	None	Acholic.
" 26	..	130	0.136	None	Acholic.
" 27	..	130	0.085	None	Acholic.
" 28	0.137	245	0.106	None	Acholic.
" 29	..	220	0.120	None	Acholic.
" 30	..	160	0.115	None	Acholic.
July 1	..	320	0.115	None	Acholic.
" 2	..	240	0.118	None	Acholic.
" 20	..	Fistula closed		None	Colored.

Two months later the patient reported some indefinite discomfort in the upper right quadrant. The blood contained 272 mg. of cholesterol per 100 cc of blood. She was given proper directions concerning the diet and was told to report again after one month's time. At the latter time she was symptom-free and her blood contained only 0.185 gm. cholesterin per 100 cc of blood.

In the severer cases the symptomatology is similar; pain, however, is more prominent. The pain is located on the right side of the abdomen high up over the liver region. It is fairly constantly present and is persistent; its intensity is variable but is usually not extreme. No enlargement of the liver can be made out; the liver is usually not tender; jaundice is not present. The notes of Case X are illustrative.

Case X.—In a married woman aged thirty-five years, a cholecystectomy without bile drainage had been done for a dilated gall-bladder packed full of stones. One year later the woman reported that she was having attacks of cramps almost every four weeks without vomiting, jaudice or fever: the attacks always subsided spontaneously. The blood contained 2875 mg. of cholesterol per 100 cc. During the following year it proved difficult to keep her free of symptoms (sometimes it was impossible to make her follow directions) and a year later she still reported having similar symptoms; at that time the blood contained 237 mg. cholesterol per 100 cc.

It is very likely that if this patient had received the benefit of a prolonged biliary drainage that much more could have been accomplished with the dietetic measures.

In a number of patients belonging in the last group the clinical course is distinguished by the periodical or irregular occurrence of

very acute attacks referred to the right hypochondriac quadrant in which pain, similar in all respects to that of a severe biliary colic, vomiting and varying grades of jaundice form dominant features of the symptom-complex. In all of these marked degrees of hypercholesterinemia are demonstrable. Occasionally these sharp attacks are associated with chills and fever. In most of the cases a spontaneous disappearance of the symptoms takes place.

At first sight the assumption is almost invariably made that the patients are suffering from a persistence, or reformation of stones which are attempting to pass from the biliary passages. Under this impression several patients were subjected to secondary operations, and yet these explorations demonstrated that the bile passages were clear of concretions, that the ducts were widely dilated and contained a turbid bile, and that no gross lesion existed in any of the neighboring organs, especially in the pancreas. In these cases bile drainage was necessarily instituted at the operation and during the convalescence this was followed by a reduction of the cholesterol content of the blood. After recovery and discharge from the hospital the clinical course assumed similarities to those of the patients in the immediately preceding group, with the exception that the efficient control of the condition was much more difficult to attain and make permanent. In one of the patients attacks of severe pain were present at periods subsequent to each of several secondary operations apparently due to the marked disturbance of metabolism and the insufficient effect of the rigid exclusion of lipoid bodies from the diet.

The notes of the following case illustrate this type of case.

Case XI.—This married woman was admitted to the hospital on the service of Dr. A. G. Gerster in 1912. At that time the history stated that she had three attacks of pain in the right hypochondrium with jaundice and chills and fever: the last attack occurred four weeks previous to her admission. At operation one stone was found in the gall-bladder and several in the common bile duct; the bile itself was thick and grumous. A cholecystectomy was done and the hepatic duct was drained. The microscopical examination of the gall-bladder showed chronic inflammation. After a fairly uneventful convalescence she was discharged from the hospital.

Three years later, in 1915, she was readmitted to the medical side of the hospital on the service of Dr. Brill. The patient had been well until four weeks before admission when another attack of gall-bladder colic had occurred and had been accompanied by jaundice. Under conservative treatment she made a spontaneous recovery and was discharged from the hospital.

Two weeks after the last discharge from the hospital, the patient was admitted for the third time to the surgical side on the service of Dr. Elsberg. The symptoms had again returned. Under observation in the hospital a very severe attack of colic occurred and

within twenty-four hours the skin became distinctly jaundiced. The patient was therefore explored for the second time. The operative findings included: (1) A common bile duct dilated as large as one's finger; (2) a yellow bile containing numerous flakes; (3) *the absence of any concretions* in any part of the biliary passages. The common bile duct was drained.

We were just at the beginning of our studies at this time and the patient was brought to our attention at this stage of her history. Our first blood examination was made three days after operation, in the presence of a freely draining, complete common duct biliary fistula, and showed that the patient's blood contained 280 mg. cholesterol per 100 cc. Under the indicated circumstances the probabilities are almost certain that prior to operation the patient's cholesterol metabolism was most profoundly disturbed and that the amount of cholesterol in the blood was very much higher. The further study of the cholesterol metabolism during the healing of the wound and the convalescence was as follows:

	Blood cholesterol, gm. per cent.	Bile cholesterol.	
		Cc.	Gm. per cent.
Feb. 18	0.280		
" 19	..	?	0.071
" 20	..	?	0.11
" 21	0.103		
" 23	..	?	0.092
" 24	..	?	0.087
" 25	0.155	?	0.120
" 26	..	?	0.132
" 27	..	?	0.075
" 28	0.100	?	0.068
Mar. 5	0.09575		
" 10	0.130		

On February 28 there was an insignificant amount of biliary discharge: within a few days the sinus closed entirely. On March 12, when the patient was discharged, the sinus was well healed, and the patient was relieved of all symptoms. We realized that this would be one of the cases in which diet would be very necessary if one hoped to have the absence of symptoms remain permanent. The patient was therefore given full directions and was instructed to report at regular intervals for blood examinations. During the following year the latter showed the following results:

April 22, 1915	No symptoms.	Blood	= 0.1625	per cent cholesterol.
May 5, 1915	" "	"	= 0.1875	" "
" 20, 1915	" "	"	= 0.1875	" "
June 4, 1915	" "	"	= 0.1550	" "
Sept. 16, 1915	" "	"	= 0.1750	" "
Nov. 4, 1915	" "	"	= 0.1735	" "
Feb. 9, 1916	" "	"	= 0.1500	" "
April 26, 1916	" "	"	= 0.1480	" "
May 26, 1916	" "	"	= 0.1700	" "

With the exception of some functional symptoms referable to the menopause.

We did not see the patient after that until 1919. At that time she reported that she had been in good health for the entire time. At this time her blood contained 0.176 gm. of cholesterol per 100 cc.

Cases of this kind, while, perhaps, relatively few in the total number of cases seen, are most satisfactory. In order to obtain good results it is necessary that one have complete coöperation on the part of the patient in the matter of diet. In an extreme case of this kind the effect of the initial depletion of lipoid bodies from the body is most valuable in that it restores the body content of cholesterol to relatively normal proportions; then with proper dietary regulations the latter can be kept within its normal limits.

Conclusions. 1. The diathetic factor in the formation of gall stones has been greatly neglected.

2. The diathetic factor is an important cause in the recurrence of symptoms after operations.

3. The recognition of this diathetic factor is important in the treatment of cases of cholelithiasis both before and after operation.

THE USE OF SULPHUR IN THE TREATMENT OF ARTHRITIS DEFORMANS.

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In 1907, Bory,[1] and Delahaye and Piot[2] administered subcutaneous and intramuscular injections of sulphur in glycerin or olive oil, for the treatment of a variety of conditions, such as, bronchopneumonia, pulmonary tuberculosis and arthritis. Since then, occasional clinical reports, favorable and unfavorable, have appeared in the literature concerning the use of sulphur for arthritis and various painful muscle conditions.[3] [4]

In 1921 and 1922, Meyer-Bisch[5] published rather extensive papers on this subject, in which both chemical and clinical data are presented. This investigator reports remarkable recoveries and improvements of cases of arthritis deformans after a course of intramuscular injections of sulphur in olive oil.

We have studied the effect of sulphur in a number of cases of joint affections classed with arthritis deformans, including in our

studies roentgenographical observations on the affected joints. Since, in arthritis deformans, there is probably a disturbance in cartilage metabolism, it is perhaps not illogical to study the relation of sulphur, which forms so large a percentage of the constituent of cartilage, to that disease. Indeed its importance is even more emphasized since the fundamental work of Hopkins,[6] which demonstrated the activity of sulphur compounds in oxidation and reduction processes. Moreover the recent publication of Haggard,[7] showing the ease and rapidity with which sulphides and elemental sulphur are oxidized in the blood, would seem to make the study of the influence of that element upon the metabolic processes of cartilage and muscle of particular importance. Experiments upon the fate, chemistry and pathology of parenterally administered sulphur, have therefore been undertaken by the writers.

Our study, comprising a number of cases of arthritis deformans shows that, although in a certain number of cases, as seen in a table given below, improvement was distinct, yet in none of these cases were we absolutely certain that this improvement was due to a specific action of sulphur, and that similar results could not have been obtained by non-specific protein injections. In no case did the roentgen-ray plates reveal any changes in the condition of the joints involved.

Our results rather seem to justify the conclusion of Hirsch and Sternberg[8] regarding the action of protein treatment and similar therapy. They regularly observe a certain number of surprising results whenever introducing any new preparation. They believe that this is due simply to mobilization of the psychic reserve powers, under the influence of a strong stimulus and of fever. Such cures last for a few days or months, according to the energy of the patient. The individual constitution influences the action of stimulating treatment, especially the fever, more than the preparation used.

Clinical. Preparation of the sulphur used: Flowers of sulphur, 7 mg. to 1 cc, were dissolved in olive oil, free from fatty acid, and sterilized at 150° C. for two hours. Longer heating was avoided, as it turns the solution to a deep red color due to the reaction of the sulphur with olive oil or some of its decomposition products. The final product, as used, was a clear, golden yellow liquid.

Method of injection: The above solution was injected intramuscularly in the gluteal region, starting with 1 cc (7 mg.) and repeated at five- to seven-day intervals, increasing the amount by 1 cc each time until 7 or 8 doses were given.

Character of the reaction: The severity of the reaction to the injection was a rather individual one, particularly regarding the temperature. Some of the patients showed no increase of temperature, even following doses of 6 cc (42 mg.). Most of the patients, however, responded with nausea, vomiting, chills, restlessness,

general joint pains, and severe headache. The headache was often relieved by pyramidon. With the larger doses of sulphur, there was severe pain at the site of injection, lasting for several days. The pain in several cases was so severe that it required the administration of sedatives. That all these phenomena were not due to the action of olive oil was shown by the fact that control injections of olive oil by itself produced no reaction.

The result of the clinical study of 17 cases of arthritis deformans treated by the method described is presented below in tabular form. (See Table I.)

Of the 17 cases observed, 4 showed marked improvement and 4 slight improvement. The remainder were either not benefited by the treatment, or became actually worse. Even in the markedly improved cases no demonstrable changes were shown roentgenographically after treatment.

In a few of the cases, also, the blood cells were counted, and in accordance with the findings of Meyer-Bisch we have satisfied ourselves that simultaneously with the constitutional reaction there is an increase in the polymorphonuclear leukocytes (up to 24,000). We have not, however, been able to confirm the findings of Meyer-Bisch on the reduction of hemoglobin and erythrocytes.

The following cases, though included in the table, seem of especial interest and are reported more fully.

Case I.—H. B., aged fifty-two years, complained of pain in most joints and deformity.

Two previous admissions to the hospital with the same complaint, for the purpose of tonsillectomy, massage, and other treatment, resulted in no improvement. Mental apathy and depression was very marked. The patient had heard of the new sulphur treatment and returned a third time to try that. He had become progressively worse since last discharged from the hospital and reëntered the hospital a bedridden patient totally unable to move about. No active or passive motion of his extremities was possible without severe pain. The jaws could not be separated more than a half inch. There was marked deformity of most joints and considerable muscle atrophy. He weighed 85 pounds. Roentgen-ray examination showed nothing more than a decrease of bone density which results from non-use.

From October 17 to November 28, 1922, he received at intervals of five to seven days 5, 10, 15, 21, 28, 35, 42, and 49 mg. of sulphur successively. After every injection the patient complained of increased pain in his joints, headache and tinnitus. The injections were followed in eight to twelve hours by a temperature of 100° to 101° F., lasting a day or two. There was considerable soreness at the site of each injection.

TABLE NO. 1.

Case No.	Name. Hosp. No. Age.	Duration, years.	Joints involved.	Deformity.	Previous treatment.	Complications.	Temperament.	Dose in mg.	Reaction.	Final result.
I	H. B. 139010 52	2	Almost all joints of the body	Marked periarticular deformities; roentgen-ray shows lack of density; muscle atrophy marked	Tolysin; cincophen; baths; tonsillectomy; extraction of teeth	Mental depression at time of admission	Optimistic; coöperative	5, 10, 15, 21, 28, 35, 42, 49	Severe after 21 mg. and the higher doses	Marked improvement; gained 35 pounds.
II	S. W. 138599 61	?	Wrists, ankles, knees, shoulders, fingers	Slight periarticular thickenings	None	Chronic bronchitis	Neurotic	5, 10, 15, 21, 28, 35, 42	Slight; pain in joints and headache	Not improved.
III	R. H. 139322 13	2	Wrists, hands, knees, elbows	Marked periarticular deformities; roentgen-ray shows lack of density; muscle atrophy and contractions	Tonsillectomy; salicylates; extraction of teeth	Secondary anemia	Not peculiar	7, 14, 21, 28, 35	Headache; pain in joints and at site of injection	Marked improvement; gained 25 pounds.
IV	C. J. 139998 25	6	Ankles and feet	Marked periarticular swelling	Salicylates; baking; plaster casts	None	Not peculiar	14, 21, 28, 35, 42, 49, 56, 70	Very severe after 42 mg.; vomiting and chills; pain in all joints excepting deformed ones	Marked improvement; walks with out difficulty.
V	E. P. 141428 21	3	Wrists, (right) shoulder, and ankles	Roentgen-ray shows a slight irregularity of the articulating surface of right radius; uneven density carpal bones of right wrist	None	Supervention of diabetes mellitus during the course of treatment	Not peculiar	21, 35, 42, 35; 5 cc milk	Moderate	Slightly improved; walks better.
VI	M. S. 140983 57	11	Almost all joints of the body	Marked deformities; bone changes, muscle contractions, atrophy	None	None	Non-coöperative	7, 14, 14, 7, 21, 28, 35	Severe	Not improved.
VII	D. H. 140190 50	5	Elbows, knees, shoulders, feet	Roentgen-ray shows lack of density; periarticular thickenings	Tonsillectomy; arthrotomy of right knee; salicylates; massage	None	Not peculiar	7, 21, 28, 35, 42, 49, 42	Mild	Considerably improved; can walk more easily and with less pain.

VIII	A. S. 131124 28	4	Knees, ankles, hips, left elbow, wrist and hand	Bone changes and periarticular deformities; muscle contraction and atrophy	Tonsillectomy; teeth extracted; proteogen; vaccines; salicylates; tolysin, cincophen	None	Optimistic	5, 10, 28; 6 cc plain oil; 42, 35, 21	Very severe; no reaction with plain oil	Slightly less pain.
IX	L. D. 136663 55	?	Almost all joints of the body	Bone changes of wrists and hands and muscle atrophy	Cincophen	Advanced arteriosclerosis; angina pectoris	Apathetic; non-cooperative	7, 14, 28, 35, 42, 49	Very slight	Not improved; deformity progressing.
X	S. O. 137362 52	5	Wrists, hands, shoulders, elbows, knees	Periarticular swellings; roentgen-ray shows a roughening of the articular surfaces of the knee-joints	Salicylates; proteogen; diet; heat; vaccines	None	Optimistic	5, 10, 15, 21, 28, 35, 42, 49 Second course 2 mos. later: 21, 28, 35, 35, 35	Mild	Slightly improved; pain less severe.
XI	M. D. 145237 48	2	Almost all joints of the body	Marked periarticular deformities; roentgen-ray shows bone destruction and hypertrophy	Salicylates; tonsillectomy; vaccine; proteogen	None	Optimistic	7, 14, 28, 35, 42, 49, 56, 63, 28; 5 cc milk; 8 cc milk; 10 cc milk; 14, 14	Severe with sulphur, less severe to milk	Condition worse; progressive deformity and incapacitation.
XII	L. B. Out pat. 17	7	Almost all joints of the body	Marked periarticular deformities	Salicylates; tonsillectomy; vaccine; massage	Secondary anemia; melancholia	Very depressed; non-cooperative	7, 10, 14, 21, 28	Mild	Not improved.
XIII	J. B. Out pat. 65	15	Almost all joints of the body	Marked periarticular deformities and bone changes	None	Arteriosclerosis	Non-cooperative	7, 10	Mild	Not improved.
XIV	M. K. Out pat. 50	7	Elbows, knees	Slight periarticular thickenings; roentgen-ray shows absorption of cartilage of left knee-joint	None	None	Optimistic	7, 21, 35, 42, 42, 49, 35, 49	Severe after 42 mg.	Considerable improvement for 2 months.
XV	J. S. Out pat. 44	12	Almost all joints of the body	Slight thickening of most joints	None	None	Not peculiar	7, 21, 35, 42, 42, 49, 35, 49	Moderate	Improvement for 2 months.
XVI	M. W. Out pat. 38	2	Knees, ankles, right elbow	Slight thickenings	Salicylates	None	Not peculiar	7, 14, 14, 28, 35, 42	Considerable; no chills	Marked improvement; much less pain.
XVII	J. P. Out pat. 42	3	Knees, hands, shoulders	Slight deformity of the knuckles	Salicylates	None	Not peculiar	7, 14, 14, 21, 28, 35, 42	Quite severe; no chills	Not improved.

Some improvement was noticed after the fifth injection, and from then on, the improvement was rapid. With the coöperation of the patient, physical therapy in the form of exercise and massage was rigidly enforced. The change in the patient's mental attitude, to one of optimism and coöperation was very striking and probably was a great factor in his recovery. In two months from the beginning of the treatment the patient was able to dress himself and walk a few steps. He was discharged April 7, markedly improved. He weighed 115 pounds. Roentgen-ray pictures at discharge showed no variation from those taken at admission. Eight months later the patient was able to walk without any stiffness or pain and felt very well; he then weighed 120 pounds. Periarticular deformity, however, was still present.

This case is an excellent example of the cures reported by various authors and tacitly ascribed to the effect of the drug employed, in the case of Meyer-Bisch to sulphur. Yet there is no ground for belief that any organic interference with the motion of the joints has in any way been eliminated, as the roentgen-ray plates show absolutely no difference in the appearance of the joints and whatever deformity was present previous to the "cure" is still present.

Case III.—R. H., a girl, aged thirteen years, complained of pain and deformity of joints.

Her present illness started like an attack of acute rheumatic fever two years ago. Although she apparently recovered from the acute attack, she noticed that her joints began to swell and ache. Tonsillectomy was performed at that time with no relief. The wrists, knees and hands became progressively worse so that she became bedridden.

Upon admission to the hospital there was marked deformity of both wrists, hands and knees, with severe pain on active or passive motion. There was considerable muscle contraction and atrophy. Her temperature was 100°F. Roentgen-ray showed no evidence of bone disease excepting the characteristic lack of density and some indistinctness of outline of some of the phalangeal joints.

The patient received six doses of the sulphur (in solution) as follows: 7, 14, 21, 21, 28, and 35 mg. intramuscularly at weekly intervals; but after the third dose the pain at the site of the injection, was so severe that for a time the patient refused further treatment. However, after the first injection an improvement was noticed which has continued to nearly complete recovery. When last seen, seven months after starting the treatment, the patient had gained about 25 pounds and was walking about freely, without any pain or discomfort. There is still some thickening around the joints which were affected. Roentgen-ray examination at this time revealed no visible changes in the bones.

Here, too, the effect was striking in spite of the negative radiographic findings. However, psychological factors probably had very little to do with this case.

CASE IV.—C. J., a man, aged twenty-five years, complained of pain and "swelling" of the ankles.

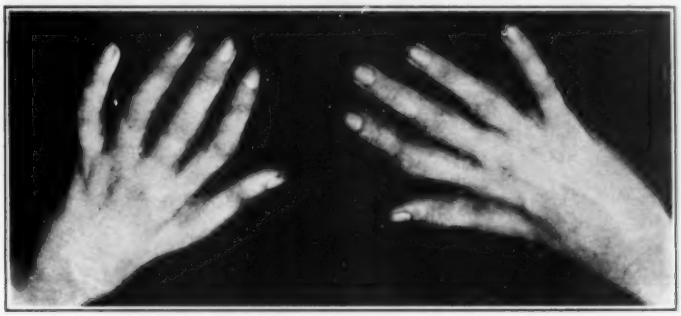

FIG. 1.—Case 3. R. H., photograph of hands showing swelling in the second phalangeal joints of the first and third fingers of the right hand before treatment.

FIG. 2.—Case 3. R. H., photograph of hands showing reduction of swelling in the joints after treatment.

The trouble began in 1917 with pain and swelling of his toes and feet which finally spread to the ankles. The condition has never affected any other joints and has become progressively worse until walking became impossible on account of the pain and thickening. Two months before admission to the hospital his feet were placed in plaster casts with slight relief of pain. Between November 28, 1922, and Feburary 6, 1923, the patient received 14, 21, 28, 35, 42, 49, 56, and 70 mg. of sulphur. After the fourth dose the patient reacted severely to each injection in proportion to the amount

FIG. 3.—Case 3. R. H., roentgenogram of hands showing periarticular swelling in second phalangeal joints of first and third fingers of the right hand before treatment.

FIG. 4.—Case 3. R. H., roentgenogram of hands showing reduction of periarticular swelling of the joints after treatment.

injected. Reactions consisted of chills, temperature of 100.5° F, vomiting, pain at the site of the injection, and, curiously enough, pain in all joints excepting in the diseased ones. After the fifth injection the pain began to abate and the swelling to disappear and

April 4 the patient was discharged improved, free from pain or deformity. Four months later he was able to walk freely and has been able to resume his work.

One cannot definitely say that sulphur did not have an influence on the diseased joint tissue in this case. The recovery is certainly noteworthy considering the comparatively long duration of the disease.

CASE XI.—M. D., a woman, aged forty-eight years, complained of swelling and stiffness of all joints excepting the hips.

Present illness: In 1921 her hands became swollen and painful and soon after her knees, shoulders, elbows and feet became involved. The condition gradually progressed until admission to the hospital, at which time walking was possible only with the greatest difficulty, due to stiffness and pain.

The patient looked forward to the sulphur treatment with greatest hope. She received 7, 14, 28, 35, 42, 49, 56, and 63 mg. of sulphur between January 12 and February 28, 1923. The most distressing features of the reactions in this case, were severe headache and pain at the site of injection.

In spite of coöperation on the patient's part, there was no improvement in locomotion or in the amount of pain, so that in March, 5 cc, 8 cc, and 10 cc of sterile milk were injected intramuscularly at five-day intervals. The reactions were identical, subjectively, to those produced by sulphur, excepting that they were not as severe and the pain at the site of the injection was not so intense.

The patient was discharged in May, unimproved, and readmitted in June when walking had become impossible. At this time the roentgen-ray plates showed partial destruction of the ends of some of the metacarpal bones, lipping of the patella, peculiar density of the articulating surfaces of the condyles of the femur, and irregularity in the outline of the astragalus and lower end of the tibia.

This case illustrates the futility of the sulphur treatment in the presence of organic hindrance to the activity of the joint even though the patient coöperated in every way.

Metabolism. In this work we desired only to test the main conclusions of Meyer-Bisch and so only a small amount of quantitative data has been collected.

Meyer-Bisch concludes that the output of urine after a sulphur injection is diminished and that there is a decided retention of chlorids. In 6 cases studied it was found that the volume of urine eliminated after the sulphur injection was subject to about the same fluctuation as before injection. Of course, when the patient developed a high temperature, there was a temporary retention of urine for about twenty-four hours. The chlorid elimination was studied under very carefully controlled diet, so that the salt output and intake could be measured. It was found that, in general, sulphur did not

cause an appreciable retention of chlorids aside from that to be expected from normal fluctuations of urine volume. It is very important to remember that the elimination of chlorids is extremely dependent on the urine volume, and that even in normal patients small fluctuations of urine volume produce large differences in salt output. The chlorid metabolism of one of our patients (A. S.) is presented in full to illustrate the above statements.

TABLE NO. 2.—CHLORINE METABOLISM. CASE A. S.

BEFORE SULPHUR.

Date.	Volume of urine, cc.	Specific gravity.	NaCl received, gm.	NaCl excreted, gm.
Oct. 28	1340	1.014	11.65	9.55
" 29	660	...	12.05	5.16
" 30	740	1.022	11.90	7.15
" 31	1220	1.008	11.50	9.68
Nov. 1	540	1.018	12.00	11.05 (?)
" 2	600	1.026	11.80	6.95
" 3	480	1.028	11.50	6.00 (Blood NaCl, 510 mg. per 100 cc)
" 4	1020	...	12.1	8.15
" 5	1500	...	11.80	10.60
" 6	920	...	12.00	6.40
Total	9020		Average NaCl received in one day, 11.83 gm.	Average NaCl excreted in one day, 8.06 gm.

Average urine volume for one day, 902 cc.

AFTER SULPHUR.

Nov. 7	920	1.024	0.65	10.30 (28 mg. sulphur)
" 9	960	...	9.96	3.40
" 12	1020	1.016	10.90	5.05
" 13	920	1.014	7.90	4.80
" 16	420 (?)	1.030	6.40	5.65
" 17	680	1.028	6.54	8.28
" 18	580	1.020	2.98	5.95 (42 mg. sulphur)
" 19	620	1.026	6.87	5.06 (Blood NaCl, 514 mg.)
" 20	1300	1.018	7.90	5.65
" 21	1200	1.018	8.54	7.20
Total	8580		Average NaCl received in one day, 6.86 gm.	Average NaCl excreted in one day, 6.13 gm.

Average urine volume for one day, 858 cc.

It will be noted that the average volume of urine per day before injection of sulphur was 900 cc, and for the same number of days after sulphur injection was 858 cc. This slight difference was insufficient to draw the conclusion that sulphur influences the urinary output. The other cases studied gave results similar to those recorded above.

In regard to the chlorid excretion, the great fluctuation of chlorid excretion with volume changes in the normal is strikingly

illustrated. This variation of chlorid excretion has been studied in a large number of normal individuals and in judging chlorid retention must be carefully considered. It will, moreover, be observed that the patient during the first twenty-four hours after injection of sulphur, instead of putting out less chlorid, actually eliminated a much larger quantity than was ingested. In fact when the amount of salt excreted for the normal period and sulphur period is compared with the amount ingested during these periods, it will be seen that the sulphur injection has actually increased and not diminished the chlorid volume (see Table 3). It will be noted that there

TABLE NO. 3.

	Normal period.	First injection.	Second injection.
NaCl ingested	106.2	73.1	26.3
NaCl excreted	69.3	49.1	24.9
Per cent excreted	43.0	67.0	91.0

was no change in the blood chlorid before or after the sulphur injection. This is evident from Table No. 2.

Meyer-Bisch states that after the injection of sulphur, a substance which is probably paired glykuronic acid is excreted. The urine of 6 patients was carefully examined polarimetrically, spectroscopically and by color reactions (phloroglucinol, resorcinol) for glykuronates over three to six sulphur injection periods. At no time could any glykuronates be detected polarimetrically, nor was the resorcinol or phloroglucinol reaction stronger than obtained from patients during normal periods. We have not been able therefore, to confirm the observation that sulphur injections cause excretion of substances giving the reaction of conjugated glykuronates and that they produce changes in the blood chemistry. There is some evidence, which is not yet conclusive, that there is a considerable diminution in the oxygen content of the blood. Thus, in 2 cases the oxygen content was reduced 21.4 per cent and 14.4 per cent respectively. The carbon-dioxide capacity remained the same.

Summary. From a review of the cases reported and the table given, it is clear that only those patients were favorably affected by the sulphur injections who showed radiographically no organic obstruction to the joint motions. The other patients, in spite of coöperation and favorable psychic influence, showed no improvement whatever; so that it is evident that sulphur cannot be looked upon as a remedy for the latter class. The question remains, however, if sulphur might have some value in the other class of cases, and if so, if its action is a specific one or not. Judging from the marked improvement of some of our patients we can understand the enthusiasm of Meyer-Bisch and others for the remedy in arthritis deformans, if indeed the class of cases remedied by sulphur could be classified with that disease. Our observations rather tend to

confirm the efficacy of sulphur in these cases; and it is not impossible if given further trial that the remedy will find its place among others for the treatment of just such kinds of joint affections, whatever they may be. Also, the absence of radiographically demonstrable abnormalities in the joints cannot exclude the possibility of the presence of some organic lesion which might after all be influenced by sulphur, although we have nothing to substantiate this.

It is however another question whether the action of the sulphur in these cases is a specific one. A number of other substances, as is well known, have been used for the treatment of arthritis, as for instance, injections of milk, sanarthrit, proteogen, and vaccines, all of which have been used, according to some observers with favorable results. All of these substances call forth a reaction on the part of the organism very similar to that of injected sulphur, although not as severe. Such results, it is accepted, are to be ascribed to the absorption of foreign proteins. The injection of sulphur, especially in the larger doses, produces a violent local reaction, with necrosis of muscle tissue and an acute inflammatory exudate extending far beyond the point of injection. Of this we have been able to convince ourselves, during the course of our experimental study on animals, which is still in progress. Absorption from the site of injection may then be responsible for the general reaction. In that case the action of sulphur would be analogous to that of non-specific proteins, with increase and mobilization of the leukocytes, which may be accompanied by the mobilization of the proteolytic ferments, as is assumed by Frederick Gay[9] in explanation of these phenomena. This question however will have to remain open until further studies are made.

Conclusions. 1. The clinical observations and the chemical data of Meyer-Bisch could not be entirely confirmed.

2. Good clinical results were obtained only in arthritis without gross bony obstruction to joint motion.

3. The use of sulphur in the treatment of arthritis gives results very similar to those obtained by the parenteral injections of non-specific proteins, and, until further studies are completed it is doubtful whether sulphur has any specific action in arthritis deformans.

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SULPHEMOGLOBINEMIA; WITH REPORT OF A CASE HAVING A DEFINITE ETIOLOGY.

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Although sulphemoglobinemia is a perfectly definite condition, presenting a clear cut clinical picture and susceptible of exact diagnosis, it is either very rare or cases are seldom recognized. Since its discovery by van den Bergh[1] in 1905, only a score of cases have been reported, and only 3 of the number have been described in this country, the others all occurring in Great Britain or Holland.

On this side of the Atlantic attention was first called to the affection by T. Wood Clarke,[2] who had observed a case in England and in 1910 established the diagnosis in the person of a young woman who was later brought to St. Luke's Hospital for further investigation. At this time some chemical studies were carried out in the case by the present writer, and in 1916 he was able to demonstrate the same abnormality in another patient, whose history is now given below. In the hope that other instances of the condition would be found, publication of this observation was deferred, but last year Mason and Conroy[3] described the second case to be put on record in this country. The writer's case was then briefly reported before the New York Pathological Society,[4] making it the third put on record here, but since that time some further publications from Holland,[5] make a somewhat more extensive discussion of the subject seem desirable.

Case Report. On February 28, 1916, a young man, F. R., presented himself for diagnosis. His appearance was remarkable in that his lips and ears were distinctly bluish in color, and his features of a livid pallor. He stated that for the past three weeks he had suffered from vertigo and fainting attacks, a rather severe seizure occurring on the preceding day. He had no headache, no pain, no intestinal nor urinary symptoms; but had been a little shortwinded for two years, which he attributed to cigarette smoking. He was employed in a chemical factory in the production of a photographic developer, para-amido-phenol, made by the electrolysis of nitrobenzene in a concentrated sulphuric acid solution, lead electrodes being used. For the past six weeks he had suffered from itching of the hands, the skin of which had now become thickened, rough and fissured. He had consulted a physician who told him he was suffering from lead poisoning. No drugs had been taken recently except some tablets containing sulphur and cream of tartar which he had been using for some time as treatment for a slight degree of

facial acne. His bowels were regular, and he suffered neither from diarrhea nor constipation.

Examination of his heart and lungs showed no abnormalities and the routine examination of the urine was negative. In the absence of any pulmonary or cardiac lesion to account for the cyanosis, the possibility of poisoning by some of the agents with which his occupation brought him into contact presented itself, notably para-amido-phenol, lead and nitrobenzene. Further tests of the urine proved the absence of phenol, urobilin, urobilinogen, or blood pigments. A blood count gave 5,200,000 red cells per c.mm., hemoglobin, 80 per cent, 10,000 leukocytes with polymorphonuclears, 76 per cent, lymphocytes, 22 per cent, and eosinophiles, 2 per cent. Examination of a smear showed no basophilic stippling of the red cells, nor anything else of note.

On spectroscopical examination of the blood, a band was plainly visible between the C and *D* lines, that is, about in the position of the characteristic band of methemoglobin, but the possibility of this being an instance of sulphemoglobinemia suggested itself and further tests were carried out. On comparison of the band in the patient's blood with the spectrum of methemoglobin produced by the action of potassium ferricyanide on a solution of oxyhemoglobin, this band was found to be further to the right than that of methemoglobin. The presence of sulphemoglobin was confirmed by the addition of a few drops of ammonium sulphide solution to each of the two specimens, when it was found that the band of methemoglobin disappeared, while that in the patient's blood remained unaffected. In order to complete the demonstration of the identity of the pigment, sulphemoglobin was prepared by passing hydrogen sulphide into a solution of normal blood until a deep violet-red color was produced. The absorption spectrum of this solution was absolutely coincident with that of the patient's blood, and the fluid when treated with ammonium sulphid also gave the characteristic reaction which differentiates sulphemoglobin from methemoglobin. These observations were carried out with a comparison spectroscope, which makes it possible to note the slightest displacement of the bands.

Further tests were then made on the serum, which was found to contain no sulphemoglobin, though with Schiff's reagent it showed the presence of a reducing substance, a control test with a normal serum being negative. Tests for nitrites by Olsen's method with sulphanilic acid and d-naphthylamin hydrochlorid were negative in the blood, the serum, and the urine, but positive in the saliva. Repeated tests on the saliva of 9 normal individuals showed that in 3 of these nitrites were present from time to time.

The patient's Wassermann reaction was negative.

He was told to stay away from work and was given cathartics. Two weeks later his appearance had greatly improved, his symptoms

had almost entirely disappeared, and the cyanosis was not very noticeable, but the sulphemoglobin was still present in marked amount.

On March 22, three weeks after his first visit, he was seen again and reported that he was feeling better and had been at work for the past three days, wearing rubber gloves as he had been directed to do in order to protect his hands from contact with the nitrobenzene. Sulphemoglobin was still easily recognizable, but was less in amount.

On May 1 he stated that he felt perfectly well, but the sulphemoglobin band, though fainter, was still unmistakable in a blood dilution of 1 to 3.

May 8. Sulphemoglobin still present.

June 26. Sulphemoglobin no longer present in the blood, and the nitrite reaction still present in the saliva, though not as strong as before. The reducing substance in the serum was still present, but much less than before.

September 28. No sulphemoglobin in the blood, and the saliva negative for nitrites.

In view of the fact that Wallis[6] ascribed etiological significance to a Gram-negative coccobacillary organism with reducing properties which he found in the saliva of 5 English cases of sulphemoglobinemia, an attempt was made to confirm this observation, and painstaking bacteriological studies were carried out by the bacteriologist of St. Luke's Hospital, Dr. L. W. Famulener. Cultures from the saliva of the patient were repeatedly made on 5 per cent blood agar, Loeffler's medium, and dextrose broth under both aërobic and anaërobic conditions and at both room and incubator temperatures. Nothing developed in these cultures, however, other than the ordinary types of mouth organisms, and no forms corresponding to the "nitrosobacillus" described by Wallis could be identified. A blood culture made on the usual media under both aërobic and anaërobic conditions gave no growth.

It is well known that cyanosis may be produced by overdoses of a long list of drugs such as acetanilid, phenacetin, trional, sulphonal, potassium chlorate, nitrites, nitrobenzol and di-nitrobenzol. In poisoning by these agents, particularly in the chronic form, there is more or less cyanosis, with headache and prostration, and but few other symptoms, unless the dose has been dangerously large, when coma and death may result. The cyanosis in these cases, which often has been attributed to cardiac depression, is really due to the formation in the blood of methemoglobin, an isomer of oxyhemoglobin which differs from the latter in having its oxygen more firmly bound, so that it is not given up when subjected to a vacuum.

A few cases have been reported, however, by Dutch or British observers in which methemoglobin was present in the blood, but no

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A few cases have been reported, however, by Dutch or British observers in which methemoglobin was present in the blood, but no

external cause for this could be discovered. To this condition the name of enterogenous or idiopathic cyanosis has been given. Stokvis in 1902[7] reported the first of these cases, and several others have since been described. Talma[8] found that in these cases the serum was clear, the methemoglobin being contained in the corpuscles only. The patients all suffered from chronic diarrhea, were markedly cyanosed, and as nitrites, which are powerful methemoglobin formers, were found in the blood by van den Bergh and Grutterink,[9] it has been believed that absorption of nitrites from the intestine was the cause of the disease. In 1 case reported by Gibson and Douglas,[10] the colon bacillus was found in the blood and these authors believed the condition to be of bacterial origin, giving it the designation of microbic cyanosis. Van den Bergh, however, reported 4 other cases, equally of unknown etiology and somewhat resembling the former group, except that the patients all were constipated, and careful study of the blood absorption bands in the spectroscope showed that the band in the red, characteristic of methemoglobin, was a little nearer the yellow than it should be. It was thus discovered that this spectrum was not that of methemoglobin, but that of sulphemoglobin, an entirely different substance obtainable by treating blood with sulphuretted hydrogen. It was also found that while a temporary disappearance of the methemoglobinemia could be produced by putting the patients on a milk diet for forty-eight hours, no change occurred under like conditions in the sulphemoglobinemia cases.

Including the present case, 21 well authenticated examples of sulphemoglobinemia are now on record, 11 from Holland, 7 from England, and 3 from the United States. Of this number only 4 have occurred in males, 2 of van den Bergh's, Mason and Conroy's, and our own; and only 4 of the patients were under twenty-four years of age. In another case in an infant reported by Willemse[11] the blood examination is not described in sufficient detail to establish the diagnosis with certainty, and it is therefore not included.

The greenish discoloration of the abdominal parietes sometimes seen in cadavers is known to be due to the postmortem formation of sulphemoglobin, and it would be a logical assumption to associate the production of sulphemoglobinemia in the living with the presence of an abnormal increase of sulphuretted hydrogen in the bowel or with the activity of sulphide-forming intestinal bacteria; but clinical observations show that the condition cannot be explained in such a simple manner. It is noteworthy, however, that stagnation of intestinal contents either through chronic constipation or owing to mechanical causes has been a feature in most of the cases of sulphemoglobinemia reported.

Clarke and Hurtley[12] in a study of the characteristics of sulphemoglobin were unable to obtain it in crystalline form, but found that it existed in aqueous solution as a definite hemoglobin derivative, and by passing acid-free carbon monoxid gas into such a solution

produced a new substance, carboxy-sulphemoglobin, with a distinctive spectrum. They also made the important observation that for the production of sulphemoglobin, conversion of oxyhemoglobin to reduced hemoglobin is an essential preliminary and that powerful reducing agents greatly accelerate the formation of sulphemoglobin from oxyhemoglobin in the presence of even minute traces of sulphuretted hydrogen. Working along these lines Wallis, who had access to 5 cases in England, endeavored to locate the source of a reducing substance repeatedly demonstrated in the serum of these patients. This substance, capable of producing reduction of the oxyhemoglobin as an essential and primary stage in the formation of sulphemoglobin, he considered might be of the nature of a hydroxylamin derivative. Its origin he supposed to lie in the activity of a "nitrosobacillus" which he isolated from the saliva of the patients and believed capable of producing the reducing agent needed to form sulphemoglobin from the sulphuretted hydrogen always present in the body in sufficient quantity in these conditions. It was with the purpose of continuing these observations by Wallis that the bacteriological studies referred to above were made in the case here reported, but with negative results. Failures to find the nitrosobacillus in the saliva are also reported by Long and Spriggs,[13] and by Mason and Conroy. It is also rather remarkable that an organism which Wallis states could not be made to grow at a temperature above 35°, and which had its optimum temperature of growth and metabolic activity at 25°, should flourish in the human mouth with sufficient vigor to produce nitrites in quantities great enough to be absorbed and give the blood strong reducing properties. Furthermore, Gies[14] and his collaborators have shown that nitrites in varying amounts are more or less constantly to be found in the saliva of healthy persons, as was shown to be the case in our own observations.

In regard to the clinical manifestations of the condition, it may be said that in addition to the cyanosis the most important symptoms are weakness, nervousness, vertigo or fainting attacks, palpitation, headache and constipation. The latter condition has been mentioned in connection with most of the reported cases, though it was not present in Mason and Conroy's case, nor in ours, and may perhaps be nothing more than a coincidence. However, 1 of van den Bergh's patients, a boy of nine years, with a rectal stricture, was cured of his sulphemoglobinemia as soon as the stenosis of the bowel was relieved, and he reports a similar result in several other cases in which a mechanical obstruction was removed by operation. After a period varying from months to years, during which the symptoms remain mild and more or less indefinite, the blue color of nails, lips, and ears, or of the entire face, develops, and still later more serious disturbances appear. These in some cases have taken the form of definite attacks of exacerbation of the

cyanosis with loss of consciousness, sometimes lasting several hours, during which the patient's condition may be very alarming.

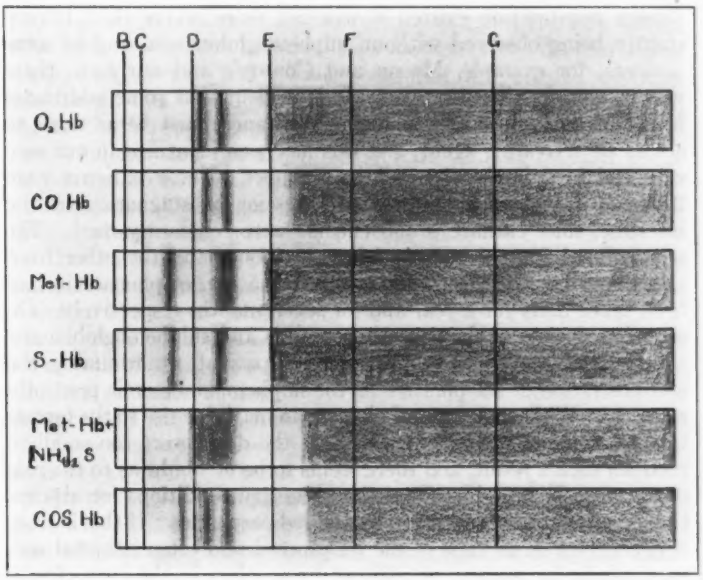
The manner in which the formation of the abnormal blood pigment is brought about is still uncertain and probably differs in different cases. Animals may be killed by the inhalation of hydrogen sulphid without the production of sulphemoglobin, and evidently two factors must gain access to the blood, sulphuretted hydrogen and a reducing substance. West and Clarke[15] have shown that only exceedingly small amounts of hydrogen sulphid are needed to produce the spectrum of sulphemoglobin, and apparently the compound is a very stable one, that once formed is not easily broken up. It is possible that the symptoms are in part produced by the anoxemia resulting, for in 1 of van den Bergh's cases from 12.5 per cent to 19 per cent of sulphemoglobin was found in the blood by gas analysis, showing that a very considerable portion of the hemoglobin had been rendered unfit for its respiratory function.

The earlier efforts to discover the source of the reducing substance needed to activate, as it were, the hydrogen sulphid of the intestine and force the hemoglobin to unite with it have been unsuccessful, but it is believed, as will be shown below, that in the author's case and in 2 others recently described by Snapper an explanation has been found applicable to these particular instances of the affection. The theory of Wallis that a special mouth organism is responsible has lacked confirmation in the cases of Long and Spriggs, Mason and Conroy, and our own, though Wallis believed he obtained good results in treatment by the use of a vaccine prepared from the nitrosobacillus. Long and Spriggs' patient improved after the removal of a carious tooth, and these authors point out that the benefit in one of Wallis' cases may also have been due to the fact that several bad teeth were extracted, but it is of interest that another patient who also improved under the vaccine treatment had had all her teeth removed nine years before the onset of the cyanosis. Free purgation and the removal of all foci of infection would seem to be the most rational modes of treatment. Although the stools of the patients are described as showing nothing abnormal, more careful bacteriological studies than have yet been made would be desirable, and possibly a vaccine from this source might prove of service.

The most important recent contributions to the subject are those of van den Bergh and Engelkes, who describe 5 additional cases and give extensive discussions of the chemistry of sulphemoglobin. A new test of identity for the substance has been discovered which consists in the fact that the addition of a 1 per cent solution of potassium cyanid causes the spectrum of methemoglobin to change at once to that of cyanhemoglobin, closely resembling that of oyxhemoglobin, but with sulphemoglobin the change requires twenty-four hours at room temperature. In their experimental work on animals these authors also made an observation of impor-

tance to future investigators, for they found that healthy rabbits apparently sometimes show sulphemoglobin. Out of 60 animals examined, 12 showed traces of sulphemoglobin, 7, larger amounts, and 4, considerable quantities, in 1 instance 10.5 per cent in the aortic blood and 12.5 per cent in the portal blood. They also discovered that in certain apparently predisposed human beings the use of sulphur-containing mineral waters may lead to a mild degree of sulphemoglobinemia.

In addition to the conditions of methemoglobinemia and sulphemoglobinemia so far referred to in which the observed blood pigment is found only in the corpuscles, a few instances are mentioned in



The absorption spectra of sulphemoglobin and related hemoglobin derivatives.

the literature in which these substances also appear to have occurred in the serum, apparently always as the result of severe infections with anaërobic bacteria. In an attempt to systematize these various groups van den Bergh suggests that the term "parhemoglobinemia" be adopted for conditions in which the blood spectrum shows a band in the red near the two bands of oxyhemoglobin, and offers the following tentative classification of what he terms the "autotoxic parhemoglobinemias."

1. *Intracorpuscular Methemoglobinemia Without Hemolysis.* In the cases reported always accompanied by longstanding and severe diarrhea, and probably of intestinal origin, with the absorption of nitrites by the blood.

2. *Intracorpuscular Sulphemoglobinemia Without Hemolysis.* Usually but not always associated with intestinal stasis.

3. *Hemolytic Methemoglobinemia.* This group appears to include a few reported cases of anaërobic sepsis and of eclampsia.

4. *Hemolytic Sulphemoglobinemia.* This has occurred in a few instances of anaërobic sepsis.

From a survey of the reported cases of intracorpuscular sulphemoglobinemia it is clear that in some instances there has been definite stagnation of intestinal contents, which would perhaps facilitate the absorption of sulphuretted hydrogen from the bowel, for example, van den Bergh's boy who was cured when his rectal stricture was relieved by operation. There are other cases, however, in which though constipation existed it was not more severe than is constantly being observed without sulphemoglobinemia, and in some patients, for example, Mason and Conroy's and our own, there was no constipation whatever. It is evident that some additional factor in the nature of a reducing substance must be at work to act as an activating agent, and this has been identified in our own case and in 2 lately reported by Snapper. These patients were 2 women in whom there was no question of stagnation in the intestine, since cathartics and enemas were constantly used. The one suffered from a metastasizing carcinoma and the other from tabes, and for the relief of pain 0.5 to 1.5 gm. of phenacetin had been taken daily for a year and for seven months respectively. On stopping the use of the drug the cyanosis and sulphemoglobinemia slowly disappeared, and in the second patient, on resuming the administration of the phenacetin, the sulphemoglobinemia promptly returned. While overdoses of phenacetin may give rise to the formation of methemoglobin, in these cases the doses were too small to produce such a result, and there seems to be no doubt as to the role of the drug in bringing about the necessary conditions for absorption of sulphuretted hydrogen by the red corpuscles. If this is true, it is conceivable in view of the widespread and often habitual use, particularly by women, of coal tar drugs, often in the form of proprietary headache cures, that some of the other reported cases of sulphemoglobinemia may be explained on this basis.

Snapper further states that he gave small doses of phenacetin (0.5 gm.) to dogs over a period of ten days without causing any change in the blood. He then administered precipitated sulphur (1.5 gm.) together with the phenacetin, and sulphemoglobinemia resulted in a day or two, while sulphur given alone produced no effect. This observation has a bearing on the conditions existing in the case of the young man here described. Unlike most of the reported patients, he had not been a sufferer from constipation, and the condition developed in connection with two special circumstances. One was that he had been taking a preparation containing sulphur, and the other that the sulphemoglobinemia developed rather quickly at a time when he was showing the evidences of

nitrobenzene poisoning in the condition of his fissured, scaly and itching hands. After he had been protected from the action of this chemical by absence from his occupation and later by wearing rubber gloves when at work, the sulphemoglobinemia completely disappeared, a behavior very different from what has generally been noted, as in most cases the affection has proved very intractable to treatment. That over two months elapsed before the blood became free from the abnormal pigment, even though the causative factors were no longer operative, is not remarkable. It has been shown that while sulphuretted hydrogen in the serum is quickly eliminated by the lungs, that bound to the hemoglobin is permanently fixed in this combination. It therefore probably exists during the life of the red cell in which it is contained, and this is now known to be from two to three months. Nitrobenzene alone does not cause sulphemoglobinemia, and it is suggested that our patient's sulphemoglobinemia was of a different type from that heretofore described, and that in this case the combination of the two factors of the ingestion of sulphur and the absorption of nitrobenzene brought about the unusual blood condition.

Conclusions: 1. Intracorpuscular sulphemoglobinemia may be brought about under a variety of conditions.

2. For its production there must be present a reducing substance which serves to make the red cells susceptible to the action of sulphuretted hydrogen derived from the intestine.

3. In some cases this activating substance is of unknown nature and may be of endogenous origin, probably through bacterial action.

4. In some cases the long continued administration of one of the coal tar drugs may furnish the necessary reducing agent.

5. Intestinal stasis favors the production of sulphemoglobinemia but is not an essential factor.

6. In the case here reported the coincidence of the ingestion of sulphur and absorption of nitrobenzene seems to explain the occurrence of sulphemoglobinemia in an individual not suffering from intestinal stasis.

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THE VALUE OF ALKALI IN DYE THERAPY.

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and

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That dyes are of value in the treatment of infections has been firmly established. The work of Churchman with gentian-violet, and that of Browning, Graham-Smith, Davis and others with many of the dyes, has determined that the dyes will eventually play a prominent part in the therapy of infected tissues.

Knowledge of the value and limitations of dye therapy is meagre. The experimental work is in the pioneer stage, and much remains to be discovered before the control and use of the dyes can be considered on a sound scientific basis. In general, the experimental work has been designed to establish the practical application and limitations of the dyes in therapy rather than to analyze the factors involved. The active fraction of the molecule of many of the antiseptic dyes is unknown, and there is little knowledge of the factors that affect the value of the dye when applied clinically. The present article represents an attempt to evaluate the effect of the hydrogen-ion concentration on the dye therapy of infected tissues.

It has long been recognized that certain factors influence the action of disinfectants. The *Report of the Committee on Standard Methods of Examining Disinfectants* specifies that the hydrogen-ion concentration, the temperature, the medium surrounding the organisms, the number of organisms, the concentration of the disinfectant and the period of exposure must be taken into consideration in estimating the value of any disinfectant.[1] It follows that these factors should be taken into consideration in developing dye therapy.

Effect of Temperature. Up to the present time little attempt has been made clinically to increase the bacteriostatic action of the dyes. Recently Churchman[2] has attempted to increase the bacteriostatic action of gentian-violet for Bacterium coli by the use of heat, at the same time calling attention to the fact that while it is a common practice to enhance the action of antiseptics by the use of heat this agent has never received much consideration or application in therapy. That the application of heat in dye therapy has serious limitations is recognized by Churchman, but he believes that the application of hot dye will be more effective than a similar application of cold dye. Churchman's experiments

show that gentian-violet at 50° C. destroys Bacterium coli in one hour, while at 35° C. it has no appreciable effect in one and a half hours.

Effect of Hydrogen-ion Concentration. The effect of the reaction of the secretions to be sterilized by the dye deserves special consideration. The control of the reaction is not subject to the same limitations as the control of heat, although extremes in acidity or alkalinity are injurious to the tissues. The tissues have greater tolerance for alkali than for acid. It is not advisable to acidify the body fluids or secretions, except to a slight extent in special fluids, like the urine, in order to increase the antiseptic power of a disinfectant. On the other hand, it is quite practical greatly to increase the alkalinity of body fluids and secretions by the administration of sodium bicarbonate, without danger of injury to the tissues. If the action of the dyes for bacteria can be increased by an increase in the alkalinity of the fluids and secretions to be disinfected, then we have at our disposal a satisfactory means of increasing the value of the dyes.

There is considerable evidence to prove that an increase in alkalinity increases the action of many of the dyes for bacteria. It remains to be determined whether an increase in bactericidal action for one species of bacteria is accompanied by an increase in bactericidal action for all bacteria. It is quite conceivable that while we are increasing the bactericidal action of a disinfectant for one species we may be reducing it, or at least not altering it, for another species. Davis[3] states that acriflavin inhibits staphylococcus and Bacterium coli in alkaline urine (pH 8.0) in a dilution of 1 to 100,000, while in an acid urine (pH 6.0) it is almost equally effective for staphylococcus, but loses most of its action for Bacterium coli.

There is also evidence to show that an increase in alkalinity decreases the bactericidal action of at least one dye, acid fuchsin and other disinfectants, such as mercuric chloride.

Graham-Smith,[4] in determining what factors influence the action of dyes and allied compounds on bacteria, demonstrated that alkalinity increased the bacteriostatic action of homoflavin and crystal-violet and decreased the action of quinone for bacteria. He concludes that the most beneficial results are likely to be obtained if the wounds are first thoroughly cleaned and the dye solution is made in a reaction at which the compound acts most effectively, provided such a reaction is not harmful to tissue. The effect of the alkali was more marked in agar than in meat extract or ox serum.

Davis and White[5] and later Davis[6] have shown that acriflavin and proflavin are more active in alkaline urine. Davis states that acriflavin inhibits staphylococcus and Bacterium coli in an alkaline urine (pH 8.0) in a dilution of 1 to 100,000. In an acid urine (pH 6.0)

it is almost equally efficient for staphylococcus but loses most of its action on Bacterium coli, a dilution between 1 to 5000 and 1 to 7500 being necessary to destroy the latter organisms. This seems to indicate than an increase in alkalinity of the urine from pH 6.0 to pH 8.0 has little effect on the antiseptic power of this dye for staphylococcus but greatly increases its action for Bacterium coli.

Browning, Gulbranson and Kennaway[7] have shown that the antiseptic action of the acridin compounds for Bacterium coli is increased in urine and peptone water with an increase in alkalinity. This action is reversed with mercuric chloride. The authors state that the antiseptic action for staphylococcus is also increased, but not to the same degree. The effect is similar whether the reaction is adjusted with hydrochloric acid, sodium hydroxide or alkaline phosphate.

Beckwith[8] has shown that an increase in alkalinity increases the action of crystal-violet in bile and saline, acriflavin in serum, brilliant green and basic fuchsin in bile, for Bacterium typhosum, and that the effect on acid fuchsin is the reverse.

Kligler[9] concludes that the reaction of the medium modifies the antiseptic action of the dyes, that the germicidal action is a function of the benzene nucleus, that the number of alkyl radicals increases the antiseptic power and that this is increased to a greater extent by an ethyl than a methyl group.

Burke[10] has shown that a solution of sodium bicarbonate improves the intensity or concentration of the dyes, gentian-violet, methyl-violet and crystal-violet, remaining in the Gram-positive organisms when stained by the Gram method. Lactic acid produced the opposite results. The suggestion is made that these facts indicate the possibility of improving dye therapy by the addition of an alkali.

The work of Burke led the authors of this paper to undertake a more intensive study of the effect of alkali in dye therapy. The present paper contains a preliminary report in order to draw the attention of clinicians using dye therapy to the possibility of enhancing the value of the treatment by controlling the hydrogen-ion concentration. There is sufficient evidence to warrant the clinical application of alkali in the treatment of infected surfaces with dyes, such as gentian-violet, crystal-violet, acriflavin, homoflavin, proflavin, basic fuchsin and brilliant green. Since the effect of alkali on the antiseptic action of many dyes has not been determined, and since the antiseptic action of some of the dyes is reduced, an indiscriminate use of alkali is not recommended.

Experimental. *Experiment 1.* To determine the effect of an increase in alkalinity on the bactericidal action of gentian-violet on a Gram-negative organism, Bacterium coli.

Technic: Samples of Dunham's peptone broth were adjusted

with sodium carbonate to the pH value of 6.6, 7.0, 7.4, 7.8, 8.2 and 8.6. Five cubic centimeters of each sample of broth were placed in test-tubes. A sufficient amount of a 1 to 200 aqueous solution of

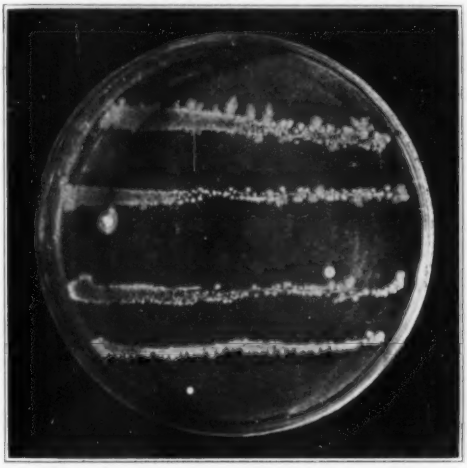

FIG. 1.—Strokes of Bacterium coli after exposure to a 1 to 1000 dilution of gentian-violet in broth having a pH 6 for one-half, one, two and three and one-half hour periods.

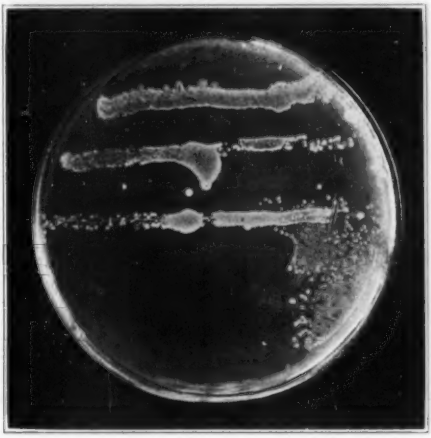

FIG. 2.—Strokes of Bacterium coli after exposure to a 1 to 1000 dilution of gentian-violet in broth having a pH 7.8 for one-half, one, two and three and one half hour periods.

gentian-violet was added to each tube to make a dilution of 1 to 1000 and also a 0.1 cc of a twenty-four hour neutral peptone broth culture of Bacterium coli. The tubes were incubated at 37° C. At inter-

vals up to three and a half hours loopfuls were taken from each tube and streaked on neutral agar. The results obtained are given in Table I, and indicate a decided increase in bactericidal action of

FIG. 3.—Strokes of Bacterium coli after exposure to a 1 to 1000 dilution of gentian-violet in broth having a PH 8.2 for one-half, one, two and three and one-half hour periods.

FIG. 4.—Strokes of Bacterium coli after exposure to a 1 to 1000 dilution of gentian-violet in broth having a PH 8.6 for one-half, one, two and three and one-half hour periods.

the dye with an increase in alkalinity. The more alkaline the broth the more rapidly the organisms were destroyed. Figs. 1, 2, 3 and 4 are of some of the plates obtained in this experiment.

The controls, made from organisms exposed to a pH 6.6 and 8.6, resembled Fig. 1. Figs. 3 and 4 indicate an individual variation of Bacterium coli in resistance to the dye. In the second streaks on Figs. 3 and 4 only a few organisms survived. Comparable results were obtained by plating out and counting the number of viable organisms per 1 cc remaining after each period of exposure. Part of the decrease in numbers may have been due to the increased alkalinity rather than to the dye since a pH 8.6 approaches the maximum range for the multiplication of Bacterium coli.

In a similar experiment comparable results were obtained with the Gram-positive organism, Staphylococcus aureus.

TABLE I.—EXPERIMENT 1: THE EFFECT OF AN INCREASE IN ALKALINITY ON THE BACTERICIDAL ACTION OF GENTIAN-VIOLET FOR BACTERIUM COLI.

Reaction.	Period of exposure in hours.			
	½	1	2	3½
pH 6.6	+	+	+	+
7.0	+	+	+	+
7.4	+	+	+	One colony
7.8	+	+	M. R.	−
8.2	+	M. R.	−	−
8.6	+	Less	−	−
Controls	+	+	+	+

+ indicates viable organisms. M. R. indicates marked reduction in the number of colonies.

TABLE II.—EXPERIMENT 2: THE EFFECT OF AN INCREASE IN ALKALINITY ON THE BACTERIOSTATIC ACTION OF GENTIAN-VIOLET FOR A GRAM-NEGATIVE ORGANISM, BACTERIUM COLI.

Reaction.	Dilution of dye.					
	1:2000	1:4000	1:5000	1:8000	1:10,000	1:20,000.
pH 6.6	−	−	−	−	−	+
7.0	−	−	−	−	−	+
7.4	−	−	−	−	−	−
8.0	−	−	−	−	−	−
8.2	−	−	−	−	−	−
8.6	−	−	−	−	−	−
Control	+	+	+	+	+	+

+ indicates presence of gas.

Experiment 2. To determine the effect of an increase in alkalinity on the bacteriostatic action of gentian-violet on a Gram-negative organism, Bacterium coli.

Technic: Samples of nutrient broth containing 1 per cent lactose were adjusted with sodium bicarbonate to the pH values of 6.6, 7.0, 7.4, 8.0, 8.2 and 8.6. Portions of each sample of broth were placed in seven fermentation tubes. Sufficient volumes of a 1 to 200 dilution of gentian-violet were added to the tubes to make dilutions of 1 to 2000, 1 to 4000, 1 to 5000, 1 to 8000, 1 to 10,000 and 1 to 20,000. To each tube was added 0.1 cc of a twenty-four-hour culture of Bacterium coli grown on neutral peptone

broth. The tubes were incubated twenty-four hours and the results read. The presence of gas served as an index to growth. The results obtained are given in Table II, and indicate that with an increase in alkalinity there is an increase in the bacteriostatic as well as bactericidal action of gentian-violet for Bacterium coli.

Experiment 3. To determine the effect of lactic acid on the bactericidal action of gentian-violet for Staphylococcus aureus.

Technic: Nutrient broth was titrated to pH 7.8 with sodium bicarbonate. Portions of this were titrated to pH 7.0 and pH 6.2 with lactic acid; 5-cc volumes of the three samples were placed in three test-tubes. To each tube was added 0.1 cc of a twenty-four-hour neutral broth culture of Staphylococcus aureus and sufficient gentian-violet solution to make a 1 to 10,000 dilution of the dye. Transplants by the loop method were made from each tube to agar plates at one-half, one and two-hour intervals. The plates were incubated twenty-four hours. The results obtained demonstrate that lactic acid reduces the bactericidal action of gentian-violet for Staphylococcus aureus. The streaks on the agar plates from the more acid tubes either failed to show growth or the number of colonies appearing was greatly reduced.

Pus frequently contains lactic acid. Dyes are reported as less effective in the late stages of infection when many organisms are present. This reduction in effectiveness may be due, in part at least, to lactic acid.

The controls in this and the other experiments demonstrated that the inhibition or death of the cells was not due to the hydrogen-ion concentration alone but to the hydrogen-ion concentration in association with the dye.

A review of the literature and of the foregoing experiments indicates that an increase in the alkalinity of the medium surrounding the organisms increases the bactericidal action of many dyes, the most important ones being crystal-violet, methyl-violet, gentian-violet, basic fuchsin, homoflavin, acriflavin, proflavin and brilliant green, for both Gram-positive and Gram-negative bacteria. It does not increase the bactericidal action of all dyes or disinfectants. The action of acid fuchsin and mercuric chloride is decreased by the addition of alkali. The fact that an increase in alkalinity increases the bactericidal action of a dye on one species of bacteria does not prove that it will increase the action on all species. However, there is no evidence to show that alkali will increase the action of a dye on one species and decrease it on another. Therefore if alkali increases the action of a dye on one species it is advisable to apply it with the given dye in the treatment of infection with other organisms. The alkali used seems to be immaterial. Sodium hydroxide, alkaline phosphate, sodium carbonate and sodium bicarbonate have been shown to increase the action of the dyes.

How Dyes Act as Disinfectants. There is some evidence to show that the bactericidal action of dyes depends upon the molecular structure, particularly the benzene nucleus. Generally the greater the number of alkali radicals the greater the toxicity of the dye. Basic dyes are in general more toxic than acid dyes. The antiseptic power is enhanced to a greater extent by an ethyl than a methyl group. The relative position of the group may be important. In the triphenylmethane dyes the bactericidal power apparently follows the double bond.[11]

It is not known how the dyes cause the death of cells or how alkali increases this action. The alkali may alter either the cell or the dye. Kligler has suggested that the effect of a change in the reaction is probably due to an alteration of the cell. The effect of the dye does not depend upon penetration, but may vary with the concentration within the cell. Burke has shown that alkali increases the amount of the dye remaining in Gram-positive organisms in the Gram-staining. Whether this result is due to a change in the cell wall, or a greater concentration of the dye within the cells, or to a change in the size of the molecules of the dye-iodin precipitate was not determined. If alkali increases the concentration of the dye within the cells this may possibly account for the increased bactericidal action. According to Langer,[12] a disinfectant is effective in proportion to the degree that it is taken up within the bacterial cell. Also the effectiveness depends upon the solution state. With increased aggregation and reduced diffusivity there is an increased disinfecting power. Alkali reduces the diffusion of a dye, and this may account for its effect on the bactericidal action.

The difference in degree of absorption by the cells may account for the difference in resistance between the Gram-negative and Gram-positive bacteria. Bacterium coli exposed to a 1 to 1000 dilution of dye may not absorb more dye than Staphylococcus aureus exposed to a 1 to 50,000 dilution. The organisms in each group, Gram-positive and Gram-negative, vary greatly in resistance to the dyes.

Effect of Hydrogen-ion Concentration on Bacteria. In estimating the value of alkali in dye therapy we must consider the effect of alkali on the various factors of infection and resistance. Our knowledge of the effect of the reaction on these factors is decidedly limited, but there is much to favor the view that alkali will prove to be beneficial in the treatment of infections for other reasons than for its effect on the antiseptic power of the dyes.

In reviewing the effect of the hydrogen-ion concentration on the growth of bacteria in the tissues and their power to produce disease we find much of interest. For each species of bacteria there is a minimum, optimum and maximum hydrogen-ion concentration for growth and for life. As soon as the reaction varies beyond the

minimum or maximum there is reduction in growth or loss of life. The optimum reaction for the most rapid multiplication of many of the pathogenic organisms is unknown. The range for growth has, in many cases, been reported. But the reaction which begins to check the rate of growth has not been determined for many of the pathogens. Before we can determine the possibility of checking bacterial action on the tissues by altering the reaction we must first determine the optimum and maximum reaction for multiplication and toxin production. Corynebacterium diphtheriæ will multiply rapidly in a reaction in which it will not produce toxin. This suggests that the reaction of the body fluids may in some cases determine the carrier state.

Recently Cohen[13] and Cohen and Clark[14] have shown that the optimum hydrogen-ion concentration for life may differ from that for growth. A change in reaction beyond the optimum has a decided effect upon both growth and life of Bacterium coli and Bacterium typhosum. The death-rate of Bacterium typhosum is at a minimum in dilute buffer solutions in the zone between pH 5.0 and pH 6.4. The pH zone for optimum growth lies between 6.2 and 7.2. It is important to note that the optimum for life (lowest death-rate) differs from the optimum for growth (most rapid multiplication). If the organisms are not multiplying they are likely to produce less serious pathological conditions in the host. It is obvious that under certain conditions in the treatment of infections our object may be attained as effectively if we aim to prevent growth as if we aim to cause death of the invading organism. If we can reduce the rate of multiplication by altering the reaction to either acid or alkaline, away from the optimum if not to the maximum, we gain something, provided such a change in reaction comes within the range of tolerance of the tissues. It remains to be determined whether a system of treatment based upon these facts can be developed. Under what conditions it is possible or advisable to alter tissue reactions in order to check bacterial activity remains to be determined.

Henderson and Palmer[15] have shown that it is possible by the administration of sodium bicarbonate by mouth to cause the urine to have a reaction of pH 8.7. This is beyond the optimum for the growth of Bacterium coli and should increase the lag, and check but not prevent the growth of the organism. The greatest acidity found in urine was pH 4.7. A change from pH 4.7 to pH 8.7 will greatly affect the antiseptic power of the dyes. The urine is normally acid and, although bladder infections with proteolytic organisms may occasionally cause it to become alkaline, it would seem advisable to administer sodium bicarbonate whenever utilizing dye therapy in the treatment of the bladder or ureter.

The hydrogen-ion concentration in some infections is antagonistic to the invading organism. The exudate in the pneumonic lung is

usually acid with a hydrogen-ion concentration of pH 6.0 or more. The pneumococcus organisms are very sensitive to acid and die in a few hours when exposed to a reaction of pH 6.0. Thus, the reaction in disease may be favorable to the host and a return to neutrality or alkalinity favorable to the invading organism in so far as the single factor of growth is concerned. However, since other factors in infection and resistance are of considerable importance it is necessary in cases of this kind to take them into consideration before reaching a decision as to the advisability of changing the hydrogen-ion concentration Also if we were adding a disinfectant, such as a dye at the time of making the reaction more alkaline we can ignore the direct effect of the changed reaction on the organisms and depend upon the dye. It is obvious that the alkali dye combination will be more effective against those organisms which are affected by the hydrogen-ion concentration used; in other words, in those cases in which the alkali checks the organisms as well as increases the antiseptic power of the dye. For this reason the limits of tissue tolerance for alkali should be reached.

Bacterial toxins, enzymes, acids and gases are important factors in disease. Their production by bacteria and their action after production is influenced by the hydrogen-ion concentration. Bacterial proteolytic enzymes act best in an alkaline medium. The optimum reaction for diphtheria toxin production lies between pH 7.2 and pH 8.0. Under other conditions there may be abundant growth but no toxin production. Diphtheria toxin is more sensitive to acid than to alkali. Botulinus toxin is not affected by acid. The peptolytic enzymes of the hemolytic streptococci are most active at pH 7.0, their action decreasing as the reaction varies to either the acid or alkaline side.[16] Proteolysis in the pneumonic lung, an important factor in recovery, is unquestionably influenced by the hydrogen-ion concentration of the exudate. These few illustrations suffice to indicate how the hydrogen-ion concentration may influence the course of an infection by affecting the growth, rate of multiplication, toxin production and enzyme action. Whether altering the hydrogen-ion concentration can be effectively utilized in the treatment of many infectious diseases remains to be determined. This will be determined partly by the difficulty of control and partly by the effect on the defensive mechanism of the body.

Effect of Hydrogen-ion Concentration on Resistance. The factors in host resistance and repair, such as complement, phagocytes and their enzymes, and fibroblast formation, are affected by changes in the hydrogen-ion concentration. Very dilute acid favors the action of most but not all ferments, and alkali is unfavorable to many of them. The action of the complement is affected by both acid and alkali. This is also true of the agglutinins antitoxin and

the amboceptor. Infectious acidosis is an important factor in recovery. In acidosis resulting from infectious diseases, such as cholera, the alkali treatment has proven beneficial. According to Sherwood, carbon dioxide, lactic acid and acetone may be present in the blood during disease in sufficient amount to favor infection or interfere with recovery.

There is evidence to show that phagocytosis and phagocytic proteolysis are affected by the hydrogen-ion concentration. Opsonins are sensitive to changes in reaction. Phagocytes and their enzymes are believed to be more effective in an alkaline than an acid medium. The intracellular proteoses of the polymorphonuclear leukocytes are more active in an alkaline medium. These leukocytes have two enzymes: One active in an acid medium, with an optimum of PH 3.5; the other active in an alkaline medium, with an optimum of PH 7.8. Both are active between PH 6.0 and 7.0. Leukocytes are said to be negatively chemotactic to lactic acid in all concentrations. They are weakly positively chemotactic to dilute sodium and potassium salts. Calcium salts increase phagocytosis.

The hydrogen-ion concentration is a dominant factor in the liquefaction and absorption of dead tissues. A septic infarct liquifies more rapidly than an aseptic infarct, due to the greater number of leukocytes in the former. Infarcts of small size are digested by the leukocytic enzymes more rapidly than large infarcts because the former are kept alkaline by blood seepage. Resolution in the pneumonic lung is due partly to leukocytic enzymes, that is, heterolysis, and partly to autolytic enzymes. Autolysis is more rapid in gray hepatization than in red hepatization, due to the absence of anti-enzymes and increase in acidity in the former. Heterolysis is more rapid in red hepatization, due to the more alkaline reaction. As indicated by these facts, the proteolytic enzymes of the polymorphonuclear leukocytes are more active in an alkaline medium and the enzymes of the tissue cells and mononuclear leukocytes more active in an acid medium. The maximum cellular autolysis of several of the tissues takes place in a PH 5.0 to 6.0. A small excess of acid inhibits the heterolysis, due to leukocytic enzymes. The reaction of the blood reduces cellular autolysis to a minimum but favors heterolysis. In autolytic organs fatty acids and lactic acid are usually present. Autolysis of cells does not begin until normal alkalinity is reduced. Autolysis can be controlled by controlling the hydrogen-ion concentration. Maximum liquefaction depends on initial acidity followed by a slight alkalinity. Since the products of protein liquefaction are toxic, it may be advisable to develop control of the rate of autolysis and heterolysis of dead tissues and exudates.

The effect of autolytic products on the invading organism is uncertain. Autolytic products are thought to inhibit bacteria, but

to what degree we are unaware. They may account for sterile pus and neutralize toxins. The autolysate of fibrin is bactericidal to staphylococcus. A rapid lysis of bacterial cells may increase the liberation of endotoxins to such an extent as to be detrimental rather than beneficial.

The hydrogen-ion concentration in the pneumonic lung is an important factor in the death of the pneumococci and in resolution. The pneumonic lung may have a reaction of pH 5.4, a hydrogen-ion concentration in which the pneumococci will live but a short time. Resolution frequently follows gray hepatization. In such cases, in which the exudate is extremely acid, the liquefaction of the exudate must be brought about largely by enzymes other than those from the polymorphonuclear leukocytes which are inhibited by acid. Thus, the acidity reduces the leukocytic action, but at the same time reduces the necessity for it by destroying the pneumococci. Too rapid proteolysis in the pneumonic lung may be detrimental. The toxic effects in pneumonia are due partly, at least, to protein cleavage rather than to bacterial secretions. Sterile suppuration has the same effect on metabolism as septic pus, due to protein cleavage. It is evident that any effort to determine the hydrogen-ion concentration of the pneumonic lung most favorable for recovery must take into consideration the effect of the reaction on the invading organism, coccus or bacillus, the effect on leukocytic action and the effect on resolution. This affords a problem worthy of intensive investigation.

The effect of a change in the hydrogen-ion concentration on the bactericidal action of some of the body fluids is known. Browning, Gulbranson and Kennaway state that alkaline phosphate added to serum *in vitro* does not affect its bactericidal action. The resistance of rabbits to anthrax infection is increased by treating the rabbits with alkali. This is not due to increased alkalinity of the blood serum (Cushny[17]). The antiseptic power of rabbit bile is increased by feeding the animals alkali.[18] Beckwith doubts the possibility of curing the typhoid carrier state by the use of alkali.[19] Urine *in vivo* can be made sufficiently alkaline to check but not inhibit the rate of multiplication of Bacterium coli and Bacterium typhosum.

Hydrogen-ion concentration is an important factor in wound healing. The healing of aseptic wounds, by first intention, requires mainly the absorption of injured cells and fibroblast formation. The secretions of aseptic wounds are alkaline. Under such conditions fibroblast formation takes place rapidly. In septic wounds the pus serum may be alkaline or acid, depending upon the organism present; pus serum usually contains lactic acid. Edema fluids are alkaline, except when bacterial activity leads to acid production. Edema, due to acid, is reduced by the blood alkali. Inflammatory exudates frequently have a hydrogen-ion concentration of pH 6.0 or more. Acid in leukocytic exudates retards leukocytic

digestion of dead tissue and bacterial cells and checks healing. It favors autolysis of dead tissue. It retards fibroblast formation and reduces the action of many disinfectants. Hyperemia is sometimes desirable in wound healing, and in these cases the treatment should be designed to bring it about if the infection does not. The autolysate of dead tissue is toxic. Dead tissue is removed by operation whenever possible and in such cases ceases to be a factor. In fresh clean wounds fibroblast formation is most important, and this is favored by an alkaline secretion. Dilute alkalies, such as some of the potassium salts, stimulate cell growth. An excess of H or OH ions leads to cell death. Mechanical injury to a cell usually results in increased acidity. A return to normal alkalinity is essential to life.

From the above discussion it is evident that the hydrogen-ion concentration has an important bearing on body resistance and repair as well as on bacterial activity or infection. Analysis shows that we are dealing with an exceedingly complex question. Whether or not in disease the reaction should be kept most favorable for the host or least favorable for the invading organism remains to be determined. In some types of infection the most favorable reaction for the host will be the least favorable for the invading organism. In other cases the reverse of this will be true. In some types of infection it might be advisable to favor the host regardless of the effect on the bacteria, and in other cases to destroy the bacteria regardless of the effect on the host. Some of the immune factors that are influenced by the reaction are more important than others. Experimentation alone will determine under what conditions it is advisable to change the hydrogen-ion concentration. This is a field of investigation in which much remains to be done. In the present article we can simply call attention to its possibilities and importance.

Effect of Hydrogen-ion Concentration on the Toxicity of Dyes for Body Cells. We have shown that alkali increases the bactericidal action of many dyes. It also favors the action of the leukocytes. It is important to know whether the increase in bactericidal action of the dye is accompanied by an increase in toxicity for body cells and to the same extent. If the bacteriotropic action of the dye is increased more rapidly than the leukocytotropic action then we gain much by the use of alkali. If the action against the bacteria and the leukocytes increases at the same rate this may necessitate a change in the dilutions used in dye therapy

Investigators are not in agreement as to whether dyes are more toxic or less toxic for body cells than for bacteria. This is important, since if dyes are more toxic for body cells than for bacteria we must consider the phagocytes eliminated as a factor in healing during the application of the dye. Infection indicates a leukocytic failure to repel the invading organism. It has been claimed that

the main function of a disinfectant is to stimulate the body defenses. It is obvious that this cannot always be true. Weak alkalis favor leukocytic action. Whether or not this will enable the leukocytes to resist greater concentrations of the dyes remains to be determined. Dyes tend to reduce the action of the phagocytes but not to inhibit it entirely in dilutions that are bactericidal for many bacteria, principally the Gram-positive organisms. The lethal concentration of most of the dyes for Bacterium coli in serum inhibits phagocytosis.[20] This statement will probably be found to hold true for Bacterium coli in acid pus and infectious exudates. Whether it still holds true after such pus and exudates are made alkaline is unknown.

The question is complex, and experimentation alone will produce a satisfactory answer. And regardless of the comparative effect on bacteriotropism and leukocytotropism we must consider the effect of alkalinization on the defensive mechanism as a whole before we can scientifically estimate the value of the alkali treatment. We believe that the ultimate fate of the dyes as chemotherapeutic agents in infection is dependent largely upon the effect and control of the hydrogen-ion concentration. More experimental evidence of the effect of dyes on body cells under tissue culture conditions and in the animal body is needed.

Methods of Application. There is evidence to show that alkali increases the bactericidal action of the dye whether alkalinization is brought about before or after the dye is added to the medium containing the bacteria. Davis has shown that the action of the dye is greater in alkaline than in acid urine. A number of investigators have reported an increase in bactericidal action, with an increase in alkalinity of broth. Presumably the reaction of the media was adjusted before the organism and dye were added. This is true in our own experiments. It has not been determined that the increase in the action is as great when the alkali is added to the dye before application. Burke has shown that the staining of Gram-positive organisms is intensified by the addition of alkali whether this is added to the organisms or to the dye before application. It seems probable that the alkali is as effective in increasing the bactericidal action of the dye whether added to the organism or to the dye just before application. However, since alkali added to the dye causes a return to the leukobase in a few hours, it seems advisable to add the alkali to the tissues before or after the dye rather than to the dye.

Body fluids can be made alkaline by the administration of sodium bicarbonate. The administration of 4 to 12 gm. of sodium bicarbonate per os will cause the urine to develop a hydrogen-ion concentration of pH 8.7 in a few hours. Two to 4 gm. three times a day keeps the urine alkaline. Urine may have a reaction of pH 4.7. A change to pH 8.7 will greatly increase the bactericidal action of

many dyes and also reduce the rate of multiplication of certain bacteria, such as Bacterium coli. The nearer the reaction comes to the limits of tissue tolerance the less favorable become conditions for growth.[21] Alkalinization of the urine should always precede the treatment of bladder and urethral infections with dyes. Davis was successful in producing antiseptic urine by the administration of sodium bicarbonate and proflavin. Whether sodium bicarbonate per os will prove effective in changing the reaction of empyema fluids and pus serum is unknown to us. If not, then an alkaline wash is indicated.

Whenever feasible infected surfaces should be cleaned of pus, blood and mucus with a good cleansing agent, such as hydrogen peroxide and then washed thoroughly with an alkaline wash. Hydrogen peroxide is slightly acid and should be neutralized with a little sodium bicarbonate before use. A slightly alkaline soap will be found beneficial in cleansing wounds, and appears to have a beneficial effect when applied to dressings. It has a tendency, however, to cause swelling of epithelial cells, and thus reduce penetration of disinfectants.

The kind and strength of alkaline wash to be used on infected surfaces should vary with the surface to be treated and possibly with the stage of healing. The more alkaline the wash the stronger the bactericidal action of the dye, but in general corrosive washes should be avoided. In the treatment of skin infections a fairly strong solution of sodium bicarbonate solution may be used. In the direct application of alkaline washes to mucus surfaces more attention should be paid to the composition and hydrogen-ion concentration of the wash. A combination of salts that are positively chemotactic to leukocytes, non-irritating and stimulating to enzymes and fibroblast formation or granulation tissue is to be recommended. Calcium ions are positively chemotactic to leukocytes. This is also true of diabasic sodium phosphate. Calcium and magnesium salts increase phagocytosis. Locke's solution is slightly alkaline, stimulating cell proliferation, and should prove to be a satisfactory wash for sensitive surfaces.

The frequency of application of the dye will be affected by the use of alkali Alkali causes a return of the dye to a leukobase in a few hours to several days, depending upon the strength of alkali used. The leukobase of a dye is less bactericidal and less toxic than the dye.

Dangers of Dye Therapy and Alkalinization. There seems to be little or no danger attendant upon the local application of dyes. In strong concentration they are slightly irritating to mucous surfaces. When applied to fresh or infected wounds there is no irritation felt by the patient. Compared with other disinfectants of equal bactericidal action the dyes are less likely to prove objectionable to the patient. Davis and others have shown that many

of the dyes are toxic when injected intravenously. Most of those that are not toxic are ineffective. At the present time the intravenous injection of dyes should be practised with caution. Not more than 5 mg. per kilo of body weight should be injected intravenously. The solution should be made up fresh in normal saline prepared from freshly distilled slightly alkaline water. Davis reports that large doses of acriflavin and proflavin *per* os when administered to rabbits are toxic but that small doses were administered over a long period without injurious effect. He reports patients complaining of nausea following a dose of 0.3 gm. but not after 0.1 gm. Uhlenhuth and Messerschmidt report methyl-violet and fuchsin as being somewhat toxic and causing necrosis at the site of injection.[22] Dyes in low concentration stimulate cell growth and may account for the development of bladder tumors. Years of contact seems to be necessary for tumor development, since none has been reported following an exposure of less than ten years. Scarlet red has been used to stimulate epithelial growth over granulation tissue.

The improper use of dyes may be detrimental to the host by stimulating bacterial activity or reducing the resistance of the host. Neufeld, Schiemann and Baumgarten[23] record that subtherapeutic doses appear to accelerate the infection. Also many of their animals died from dye poisoning. Dye therapy is in the experimental stage and, while clinical application is desirable dye therapy should be used with caution, particularly in combination with alkali therapy.

When used in great concentration some of the dyes may check healing. Mueller[24] states that under tissue culture conditions the triphenylmethane dyes inhibit tissue cells in dilutions not inhibiting streptococci. With the flavins the inhibiting dilution is the same for tissue cells and streptococci. Mueller points out that this may not be true in the body, since the conditions would be more favorable for the tissue cells and less favorable for the organisms. Russel records gentian-violet as inhibiting the growth of certain tissue cells and not others under tissue culture conditions.[25] The proper use of an alkaline wash will make conditions more favorable for the tissue cells. Since this will increase the bactericidal action of the dye there can be a corresponding reduction in the strength of the latter. The value of alkalinization will depend to some extent upon its effect on the toxicity of the dyes for tissues.

Recent articles indicate that excessive alkalinization of the body is, under certain conditions, attendant with danger to the patient. This does not apply to local application. The excessive use of alkali may lead to nausea, damage to the kidneys, with associated toxemia, depletion of body salts, and other pathological conditions.[26] However, it appears that the administration of sufficient alkali to keep the urine decidedly alkaline over a comparatively short period of time is unlikely to produce disturbances in the average patient.

Conclusions and Summary. 1. The bacteriostatic and bactericidal action of many of the dyes varies with the hydrogen-ion concentration of the medium surrounding the organisms. With an increase in alkalinity there is, with but few exceptions, an increase in the action of the dyes for Gram-positive and Gram-negative bacteria.

2. The fluids of the body may vary in their hydrogen-ion concentration from pH 4.7 to pH 8.7 or more. The bactericidal action of the dye varies greatly within this range. The body fluids should be made alkaline by the administration of sodium bicarbonate or the application of an alkaline wash before the dye is applied

3. Lactic acid, which is usually present in pus, reduces the action of the dyes.

4 The bacteriotropic action of the following dyes can be increased by the use of alkali: Crystal-violet, methyl-violet, gentian-violet, brilliant green, basic fuchsin, the flavins, malachite green. The action of many other dyes of less importance is affected in the same way.

5. The use of alkali will in certain types of infection prove beneficial in addition to the effect on the antiseptic power of the dyes. Controlling the hydrogen-ion concentration of the body fluids may be utilized to check the growth of certain bacteria. Many of the factors in resistance and repair, such as the leukocytes, certain enzymes, fibroblast formation, etc., are more active in an alkaline medium.

6. The action of dyes as disinfectants, methods of controlling the hydrogen-ion concentration and the dangers attendant upon alkalinization and dye therapy are discussed.

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THE HEMATOLOGICAL RESPONSES TO INJECTIONS OF STREPTOCOCCI.

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The primary object of this investigation was to study the changes produced in the blood stream and hemolytopoietic organs by hemolytic streptococci; but the changes manifested were of such a nature

that a subsequent study of the changes produced by the viridans and non-hemolytic types also became necessary.

It has been observed that in streptococcus infections there is frequently a decrease in the number of erythrocytes and amount of hemoglobin, and that at autopsy the blood often seems to have undergone lytic changes. The first mentioned effect has not had sufficient study. Whether the lytic is terminal or, possibly even postmortem, has never been established; yet it has been used as evidence for hemolysis *in vivo* by streptococci.[1 2]

We have attempted to control the experiments by obtaining definite data before the infection, and by following the progress of the infection by observations at specified intervals. In this way the results obtained offer tangible evidence regarding the presence or absence of blood destruction and bone-marrow irritation *in vivo*.

Experimental. Rabbits were used exclusively for the injections. The animals were selected on the basis of good physical condition in order to exclude as far as possible extraneous factors. Injections were made intravenously with different strains of streptococci which had been grown for fifteen to sixteen hours in meat infusion broth, the initial reaction of which was PH 7.8. The work was so arranged that one ear was used to receive the injections and the other for bleeding purposes. As a rule animals were injected several times so that the bone-marrow would produce indication of irritation or stimulation. The blood of the animals was examined several times before inoculation. This examination consisted of an enumeration of the erythrocytes and leukocytes (Levey Hemocytometer), a differential count, and an estimation of hemoglobin (Sahli). In making a differential examination of the leukocytes, smears were made in the usual manner, stained by any one of the various methods (Wright, Giemsa, Leishman), and 250 leukocytes counted. After injection, identical blood examinations were made at four, eight, and twelve hours; but later the twelve-hour examination was omitted since it did not materially add to the data. In case of Streptococcus viridans experiments, the serum was tested for the presence of methemoglobin by means of a microrefractometer so that the amount of serum required would be small and would not affect the red blood count. The examinations were then continued, usually every twenty-four hours after the injection.

The experiments sought to determine the effect of an infection due to: (1) A virulent and strongly hemolytic strain; (2) a highly virulent strain with hemolysis as a secondary consideration; (3) a hemolytic laboratory stock strain to produce, if possible, a subacute or chronic condition; (4) a viridans strain; (5) a non-hemolytic strain.

EXPERIMENT I. *Infection induced by a virulent and hemolytic strain; its hemolytic character being the primary consideration.*

This rabbit was inoculated with 2.5 cc of a sixteen-hour culture of a strain isolated from the blood culture of a fatal case of puerperal sepsis. Several injections were made.

TABLE I.—SHOWING THE EFFECTS OF A VIRULENT AND STRONGLY HEMOLYTIC STRAIN.

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection . .	63	4,390,000	5,300	37.5	54.0	4	2.5	1.0	1.0	1290
4 hours after injection	50	3,860,000	6,400	70.0	25.0	3	1.0	1.0	0.0	1294
8 hours after injection	45	2,770,000	10,000	77.5	17.5	1	0.0	3.0	0.0	1290
24 hours after injection	50	4,400,000	7,800	37.5	59.5	2	0.0	0.0	1.0	1284
Before injection . .	48	3,900,000	8,280	43.5	41.0	3	12.0	0.0	0.0	1284
4 hours after injection	46	3,500,000	3,600	69.0	21.0	1	8.0	0.5	1.0	1274
8 hours after injection	42	2,900,000	6,400	73.0	10.0	0	5.0	0.0	12.0	1274
12 hours after injection	42	3,140,000	4,000	51.0	36.0	6	1.0	0.0	6.0	1291
24 hours after injection	42	3,410,000	5,200	38.0	41.0	0	9.0	0.0	12.0	1252
48 hours after injection	48	3,400,000	12,400	40.0	50.0	2	3.0	0.0	5.0	1200
Before injection . .	46	3,700,000	18,500	39.0	43.0	5	5.5	0.0	7.5	1176
4 hours after injection	46	3,760,000	12,200	43.0	45.0	1	9.0	0.0	2.0	1156
8 hours after injection	40	3,800,000	7,500	76.0	20.0	1	1.0	0.0	2.0	1156
24 hours after injection	33	3,200,000	20,600	41.0	48.0	1	6.0	0.0	4.0	1114

This animal died on the second day after the last examination (that is, lived six days). Hemolytic streptococci were recovered from the heart blood, peritoneum, spleen, and bone-marrow. Marrow from the femur was reserved for study.

This experiment was repeated with two other strains, one isolated at necropsy in a case of myocarditis; the other from a pleural fluid following pneumonia. The results were of the same nature with the exception that the leucopenia following each injection was more severe.

EXPERIMENT II. *Infection induced by a highly virulent strain; hemolysis being a secondary consideration.*

This rabbit received 2 cc of a fifteen-hour culture of a hemolytic streptococcus isolated from the gastric contents of a case of carcinoma of the stomach. The results are given in Table II.

The rabbit died between the forty-eighth and seventy-second hour. Hemolytic streptococci were recovered from cultures of the heart, peritoneum, spleen, and bone-marrow. This experiment was reproduced by the injection of a streptococcus isolated after death from endocarditis.

TABLE II.—SHOWING THE EFFECTS OF A STRONGLY VIRULENT AND HEMOLYTIC STRAIN.

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection . .	55	4,180,000	10,000	50	45	2	1	0	2	1440
4 hours after injection	48	3,910,000	7,900	80	19	1	0	0	0	1447
8 hours after injection	45	3,450,000	6,040	69	27	1	3	0	0	1443
12 hours after injection	45	3,550,000	13,600	50	32	3	11	0	4	1421
24 hours after injection	45	3,800,000	21,800	79	17	1	3	0	0	1415
48 hours after injection	45	3,900,000	17,000	68	29	1	1	0	1	1365

TABLE III.—SHOWING THE EFFECTS OF A LABORATORY STRAIN (HEMOLYTIC).

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection . .	85	5,200,000	5,100	40	51	7	1	1	0	
1 day after injection .	61	5,270,000	9,400	45	39	7	4	1	3	
2 days after injection .	50	4,500,000	8,200	45	39	4	7	0	3	
1 day after injection .	50	5,400,000	8,200	53	30	4	6	0	5	
2 days after injection .	46	4,800,000	13,800	46	42	4	5	1	4	
3 days after injection .	46	4,750,000	7,800	58	33	1	7	1	0	
Before injection . .	52	5,400,000	8,200	58	43	4	3	0	2	
1 day after injection .	52	4,470,000	8,200	58	38	3	6	0	0	
2 days after injection .	52	5,200,000	7,800	38	51	4	4	0	2	
3 days after injection .	57	5,230,000	17,500	71	21	0	4	0	4	
Before injection . .	58	5,450,000	7,400	45	49	2	1	0	3	
1 day after injection .	56	5,280,000	4,600	45	49	2	1	0	3	
2 days after injection .	56	5,760,000	8,400	54	42	2	1	0	1	
Before injection . .	60	5,700,000	9,200	45	51	2	0	0	2	
1 day after injection .	64	5,660,000	5,600	37	60	0	1	0	2	
4 days after injection .	70	7,000,000	12,000	40	53	2	3	1	1	

EXPERIMENT III. *Infection induced by a laboratory strain to approximate a subacute or chronic condition in man.*

This strain was isolated more than a year ago from pus. It has a high hemolytic titer, and we assumed its virulence to be of a

low grade. Broth cultures (incubated fifteen to sixteen hours) were injected intravenously in 1 cc amounts, and the injections were continued regularly twice a week for about three weeks.

The animal died one day after the final blood examination (that is, lived twenty-eight days). Hemolytic streptococci were recovered from the peritoneum, heart blood, spleen and bone-marrow.

Analysis of the Effects of Hemolytic Streptococcus Injections. A study of the tables shows several facts. In the first place there is a loss of erythrocytes accompanied by a concomitant decrease in hemoglobin. This loss is rapid and extensive, usually taking place within eight hours, and in some cases constituting 50 per cent of the original number of red cells. But this reaction is transient and within twenty-four hours the number of erythrocytes is approximately normal. The hemoglobin, although tending to return toward normal, never reaches the normal. This is particularly true after the first injection, but as the injections are continued the loss of blood cells becomes progressively less, so that the level remains relatively constant. At the termination of the experiment the number of red cells is appreciably less than at the beginning. In Experiment I, these results are clearly demonstrated; but if the strain happens to be too virulent, the hemolytic effect is either masked or is of less degree because death occurs too soon for any great changes. On the other hand, a non-virulent strain produces only a slight decrease in erythrocytes.

Just as significant are the leukocyte reactions. The general rule is, first a decided leukopenia, in some instances to 70 per cent of the normal. The period of leukopenia varies but usually reaches its lowest in eight hours. This is followed by a sharp leukocytosis; the leukocytes manifest this reaction with each succeeding injection of the streptococci, and if anything the leukopenia becomes more accentuated. The differential count shows a decided preponderance of amphophiles (the counterpart of polymorphonuclears of the human blood) frequently reaching 80 per cent or more. This is especially significant when one considers that normally rabbits show 40 to 50 per cent amphophiles. The sudden appearance and disappearance of basophiles is puzzling. They fluctuate within wide limits, and their fluctuations are not interpretable in terms of frequency or corelationship to any of the controllable factors.

The weights of the animals show many variations, which do not appear associated with loss or recovery of blood cells. In those animals which ultimately succumb the mean of the weight curve tends lower and lower; in cases of recovery from the infection, the weight lost is gradually regained.

When the infection extended over a prolonged period blood destruction was evident in the blood smears as in Experiments I and III. Anisocytosis and poikilocytosis generally appeared, the former preceding, and polychromatophilia also occurred. Occasionally

normoblasts were discovered, though it must be said that their number never exceeded 3 per cent and they appeared and disappeared in an unexplainable way. Leukocytes were often found that had undergone disintegration, but there was a doubt as to whether this was a result of the injections or mechanical. Myelocytes, in small numbers, were seen occasionally. In some of the four-hour smears, streptococci were often present, both unattached and within white cells. When death occurred shortly after the injection (Experiment II), the smears were normal except for the differential percentage.

The marrow reactions were by far the most important produced and were distinctive of the type of infection.

In Experiment I the marrow suggested a hypoplastic condition. There was apparently an extensive destruction of both red and white cells. The cells that were present stained poorly and were undergoing swelling and karyorrhexis. Some leukoblasts and primordial red cells were distinguished, but no eosinophiles nor basophiles were discoverable. The general appearance suggested that there had been a powerful irritation followed by an exhaustion of the erythropoietic organs.

The changes of the second type of infection were distinctive of an extremely toxic condition. Eosinophiles predominated and most of them were undergoing degeneration. A fair number of normal erythrocytes were present, so that it would seem that the toxic rather than the hemolytic character of the streptococci injected was the most important factor. Karyokinesis was observed in occasional cells.

The third type showed an actively progressing regeneration. There were nucleated erythrocytes in all stages, and karyokinetic cells were frequent. There were no changes in the leukocytic cells and the eosinophiles were not abnormally numerous. In short the picture was one of active hemopoiesis.

It is evident that hemolytic streptococci exert a destructive influence on erythrocytes and leukocytes. In order to show that this action is specific and not perhaps due to a foreign body, or a redistribution of the blood away from the peripheral circulation, and so on, rabbits were injected with cultures of Streptococcus viridans in one case, and non-hemolytic streptococcus in the other.

EXPERIMENT IV. *Infection induced with Streptococcus viridans.*

This strain was isolated from a pneumonic sputum and 3 cc of a sixteen-hour culture was injected. The results are presented in Table IV.

EXPERIMENT V. *Infection induced with a non-hemolytic strain* (Table V).

This strain was isolated from a human blood culture, a few days preceding death. Three cubic centimeters of a sixteen-hour culture were injected.

TABLE IV.—SHOWING THE EFFECTS OF VIRIDANS STRAIN.

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection . .	80	5,400,000	7,400	32	60	3	5	0	0	1872
4 hours after injection	77	5,420,000	5,000	74	19	0	5	0	0	1872
8 hours after injection	65	4,890,000	4,500	76	16	0	7	0	0	2020
24 hours after injection	75	5,350,000	7,300	46	48	1	5	0	1	1875
Before injection . .	75	6,360,000	15,400	35	57	2	4	0	0	1880
4 hours after injection	75	6,480,000	4,640	30	59	1	7	0	4	1896
8 hours after injection	70	5,650,000	20,200	53	39	0	7	1	2	1896
12 hours after injection	75	5,470,000	6,900	45	49	1	3	2	3	1898
24 hours after injection	78	5,800,000	8,600	35	49	3	8	0	1	1908
Before injection . .	75	5,400,000	9,200	41	48	4	5	0	2	1910
4 hours after injection	75	5,290,000	6,800	78	14	1	4	0	1	1910
8 hours after injection	70	4,750,000	5,000	75	18	1	4	3	0	1916
24 hours after injection	75	5,380,000	14,800	51	27	4	16	2	0	1880

(This rabbit did not die.)

TABLE V.—SHOWING EFFECTS OF NON-HEMOLYTIC STRAIN.

Time of examination.	Hemoglobin, per cent.	Total erythrocytes.	Total leukocytes.	Differential percentage.						Weight, gm.
				Amphophiles.	Lymphocytes.	Mononuclears.	Basophiles.	Eosinophiles.	Transitionals.	
Before injection . .	65	4,280,000	8,600	48	51	1	0	0	0	2060
4 hours after injection	63	4,400,000	4,400	60	37	2	1	0	0	2052
8 hours after injection	63	4,010,000	7,500	70	24	2	3	0	1	2030
24 hours after injection	65	5,130,000	9,500	62	25	1	7	0	0	1980
48 hours after injection	65	4,340,000	9,300	66	26	1	3	1	3	2050
96 hours after injection	X	4,960,000	11,600	45	45	1	5	1	2	1900
Before injection . .	68	4,720,000	8,000	40	46	5	4	0	2	1955
4 hours after injection	68	5,100,000	4,000	76	18	1	4	1	0	1916
24 hours after injection	68	5,030,000	6,400	36	46	6	12	0	0	1957
48 hours after injection	65	5,100,000	10,500	24	63	3	3	0	7	2079
5 days after injection .	65	4,870,000	8,200	33	60	2	2	0	3	2160
7 days after injection .	65	4,280,000	6,000	33	60	1	4	0	2	2185
Before injection . .	68	5,430,000	7,100	35	60	0	5	0	0	2100
6 hours after injection	60	4,910,000	2,300	76	17	0	7	0	0	2185
24 hours after injection	60	4,750,000	6,000	26	68	1	5	0	0	1933
96 hours after injection	60	4,510,000	10,600	27	70	1	2	0	0	2005

(This rabbit did not die.)

The experiment with Streptococcus viridans was repeated with a strain from pus, and showed more or less the same tendency; with the repetition of the non-hemolytic experiment queer results were obtained. In one case, the rabbit responded as shown in Table V; but in the other instance, an anemic condition was produced, a decided destruction of red cells, a decrease in hemoglobin, anisocytosis, poikilocytosis, polychromatophilia, a discharge into the circulation of nucleated reds, and what appeared to be basophilic megaloblasts. These results were so different from those obtained in the other two similar experiments and so unexplainable that it was felt that they were probably referable to some preëxisting condition in this animal.

To summarize Experiment IV, it can be stated that the destruction of red cells and the decrease in hemoglobin are slight. There seems to be a slight loss in erythrocytes within eight hours, but it is not large enough to be definite. The leukocytes show the same picture as in the case of hemolytic streptococcus injections. Methemoglobin was not demonstrated in the serum.

In Experiment V the red blood cells and hemoglobin do not appear to have been affected by the organisms injected. The slight changes were within the normal variations. The leukocytes show a leukopenia, followed by a leukocytosis with a preponderance of amphophiles. The basophiles in Experiments IV and V show a similar inexplainable appearance and disappearance as in the case of hemolytic streptococcus injections.

Discussion. In this discussion, two points must be borne in mind: first, that as injections of organisms are repeated, the animal is becoming more and more immune; and second, that an originally virulent strain loses its virulence as it is kept on laboratory media. The result is that the first injection may show enormous changes in the blood picture, while subsequent injections may show progressively less changes until perhaps there are no longer apparent effects. In attempting to produce a chronic condition (as in Experiment III), this difficulty was particularly encountered. The animal no longer showed response to the injections and as a matter of fact eventually compensated for the original loss of erythrocytes; then as the injections were continued, no further changes were obtainable.

It is patent that blood destruction may accompany injections of hemolytic streptococci. It cannot be considered as due to a redistribution of the blood away from the peripheral circulation, nor to a foreign body reaction. The fifth experiment with non-hemolytic streptococci shows clearly that the reaction is peculiar to those cocci which possess the ability to destroy blood. This blood destruction we regard as referable to the soluble hemolysin contained in the cultures. First the cultures used were young, and as De Kruif and Ireland[3] have shown, it is from such cultures that the greatest yield

of hemolysin is obtained. Secondly, the destruction was rapid and was succeeded by a compensatory reaction which might indicate that the hemolysin contained in the broth culture was eliminated from the circulation, bringing the lytic action to an end. It is quite true that Hopkins and Parker[4] demonstrated that streptococci injected into the blood stream are no longer recoverable after a few hours, but their reappearance is equally positive. After the first destruction of red cells, there is an overproduction tending to bring the count toward the normal, despite the fact that streptococci are still in the circulation. The increase in number of erythrocytes before death (as in Experiment III) is possibly explained by dehydration due to fever, combined with lack of food and water intake, concentrating the blood constituents.

The hemoglobin decreased, though not proportionately with the red cells. But after the initial destruction of cells, an increase in their number was never accompanied by a corresponding increase in hemoglobin. This is explainable on the grounds that in cases of rapid destruction of red cells, there is regeneration of an abnormally large number of cells, which do not contain normal amounts of hemoglobin.

The leukopenia reported here had already been observed by Hopkins and Parker[4] and Tongs.[5] This leukopenia is accounted for, we think, partly by the presence of a leukocidin in the cultures used for the injections. It has been clearly shown by Nakayama[6] that ten- to twenty-four-hour cultures contain a leukocidin, although the presence of such a substance had long been suggested by Ruediger,[7] Hektoen,[8] McLeod[9] and others. Tongs, also, suspecting a leukocidin responsible for this leukopenia demonstrated micro- and macroscopically that his cultures (twenty-four hours old) contained this toxic material. There is another possibility which may contribute to the leukopenia. The injection of a foreign body may draw the leukocytes from the peripheral circulation within a few hours and then produce a discharge of the leukocytes plus newly generated ones, thereby producing the leukocytosis. Such an assumption better explains such a case as Experiment V, where no action on the blood (except for this one of leukopenia) can be demonstrated either *in vitro* or *in vivo*.

The types of red and white cells observed by smear are of interest. The red cells show in some cases extreme variations in shape, size and ability to take the basic stains, thereby suggesting anemic changes. We should hesitate to state, however, that these changes are anemic. Fishel and Adler[10] reported that they were able to produce pernicious anemia with a hemolytic streptococcus isolated from a human case with this diagnosis. Normal rabbits frequently show these atypical red cells, so that their appearance is not necessarily significant. The fact that the number of red cells decreases so much and no more, that nucleated reds in the circulation are

few, that the more embryonic reds are very rarely seen, and that an immunity is developed, leads us to surmise that a chronic clinical anemia produced by streptococci would be a very unusual thing.

The basophiles in the smears examined were beyond explanation by us. We could not coördinate either their sudden increase or their sudden decrease and disappearance. Basophiles normally are present in rabbit's blood averaging about 6 per cent, but increases to 12 to 15 per cent and a decrease to 0 were common.

The bone-marrow offered the best field for study. It acted in a sensitive way to the injections and perhaps explained the reactions taking place most clearly. It would appear that hemolytic streptococci will produce blood destruction *in vivo* provided the strain used is virulent or the dosage of an avirulent strain is extremely large. If the strain is excessively virulent, the destruction is not marked (due to rapid death). When death occurs it is probably caused by a toxemia plus blood destruction, rather than blood destruction alone.

Summary. Rabbits were injected with different strains of streptococci to determine their effect on the blood. Three types of infections were attempted with hemolytic streptococci and these were controlled by injections of the viridans and non-hemolytic types.

Hemolysis occurred *in vivo* by injection of young cultures of Streptococcus hemolyticus. Virulent hemolytic strains produced the best examples; strongly virulent strain produced death rapidly and the blood changes were less extensive; with a laboratory strain, the changes produced were the best of the three types.

Viridans strains produced slight hemolysis.

Non-hemolytic strains did not produce blood destruction.

All three types of streptococci produced first a leukopenia which was followed by a leukocytosis. The leukopenia was due either to the presence of leukocidin, or to a foreign body reaction, or perhaps to a combination of both. The leukocytosis showed a preponderance of amphophiles.

Basophiles appeared and disappeared in an inexplainable way in the blood smears.

The marrow offered the clearest picture regarding blood destruction, blood regeneration and toxic effect of the streptococci injected.

Since going to press, we have determined more definitely the nature of the blood destruction and leukopenia. Sterile filtered cultures of hemolytic streptococcus in two out of five instances produced a decrease in red cells and hemoglobin. This reaction was not so extensive nor of so long duration as when whole cultures were injected.

Rabbits injected with foreign protein, such as horse serum, typhoid vaccine, Coley's fluid and casein showed the same type of leukocyte changes as did the cultures of streptococci. We believe, therefore, that the leukopenia and leukocytosis are foreign protein reactions rather than specific of streptococci.

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REVIEWS.

A Manual of Chemistry. By W. Simon, Ph.D., M.D., late Professor of Chemistry, College of Physicians and Surgeons of Baltimore; and Daniel Base, Ph.D., formerly Professor of Chemistry, Maryland College of Pharmacy. Twelfth edition. Pp. 667; 55 engravings and 7 colored plates. Philadelphia: Lea & Febiger, 1923.

In the words of the preface, "The object of this manual is to furnish to the student in concise form a clear presentation of the science, an intelligent discussion of those substances which are of interest to him, and a trustworthy guide to his work in the laboratory." After a short section on the fundamental properties of physics and on heat (under the head of Chemical Physics) the book is divided into sections of General Chemistry (303 pages), Analytical Chemistry (70 pages) and Organic Chemistry (209 pages). It should be a valuable help to students of medicine, pharmacy and dentistry, for whom it has been especially adapted. K.

Green's Manual of Pathology and Morbid Anatomy. Revised and enlarged by W. Cecil Bosanquet, M.D., F.R.C.P., Physician to Charing Cross Hospital; and G. B. Wilson, M.D., M.R.C.P., Demonstrator in Bacteriology, Charing Cross Hospital Medical School. Thirteenth edition. Pp. 624; 244 illustrations. Philadelphia: Lea & Febiger, 1923.

Any medical book that has reached its thirteenth edition must *ipso facto* possess marked intrinsic value. In the present case we suspect that this value must be largely in the excellent reputation of the early editions and in the attractive form in which this edition is presented. The illustrations are examples of the latter virtue, especially those from the C. C. H. museum; but, on the other hand, too many are from the Ziegler-Rindfleisch era. Unless the difference in teaching pathology in Great Britain and in this country is greater than commonly thought, the book should seem old-fashioned and not sufficiently up to date to readers of both

countries. For instance, the only mention of the glands of internal secretion is found under the head of "auto-intoxications," where the pituitary is dismissed in 14 lines, the ovaries in 13, the testicles in 6—exactly the same number as is devoted to "sapremia," though it is admitted on page 292 that "pure sapremia . . . rarely, if ever, occurs, and the term has little real significance." More than 100 pages are devoted to bacteriology and immunity, which causes all of special pathology to be condensed into 206 pages. Diseases of the spleen are thus dismissed in less than a page, functional disorders of the heart in a half-page (of which the arrhythmias get 9 lines) and so on. Although such criticisms lose force when applied to a manual, we feel that they correctly emphasize its value relative to more complete books. For those who desire the smaller kind, this book is not without merit.

K.

PRURITUS OF THE PERINEUM. By JOSEPH FRANKLIN MONTAGUE, M.D., of the Rectal Clinic, University and Bellevue Hospital Medical College; Fellow American Proctologic Society and New York Pathological Society. Foreword by DR. GEORGE DAVID STEWART, President of the New York Academy of Medicine. Pp. 181; 37 illustrations. New York: Paul B. Hoeber, 1923.

ANYONE who has struggled with the treatment of pruritus of the anus and vulva will welcome a small monograph devoted to the condition. There is a wealth of information on the history, pathology, etiology, clinical characteristics and treatment. The author defines two groups; namely, indirect pruritus and direct pruritus. The book is devoted largely to elucidating his concept of indirect pruritus which is his contribution to the etiology. This form of itching is due, according to his ideas, "to the perception of the pruritic sensation which in consciousness is referred to the pruritic zone, an area which is at the inception of the pruritus devoid of any pathology at all. This phenomenon is due to the transference of an irritable stimulus from the visceral afferent nerves to a normal somatic afferent nerve channel or pathway and the consequent misreference or error in localization." This concept is, naturally, impossible of definite proof or disproof but is supported by analogy and clinical instances of cure by removal of visceral disease. It has the merit of demanding thorough general examination and treatment. Direct pruritus is dependent upon local disease and may follow indirect pruritus as a result of trauma from scratching or irritating applications. Treatment is fully considered and a complete bibliography is appended.

P.

HIGH BLOOD-PRESSURE: ITS VARIATIONS AND CONTROL. By J. F. HALLS DALLY, M.A., M.D., B.C. (CANTAB.), M.R.C.P. (LOND.), Physician to the Mount Vernon Hospital for Tuberculosis and Diseases of the Heart. Pp. 155; 23 illustrations. New York: William Wood & Co., 1924.

THIS work deals with the clinical estimation of the arterial pressure, and the etiology, pathology and treatment of hypertension. The importance of the diastolic pressure is emphasized throughout, and the evidence is reviewed upon which the end of the third phase is taken as the true index of the diastolic pressures. A bibliography of 193 references concludes the book. Even though one may question the need for another book upon hypertension at this time when so little is known regarding its cause or cure, nevertheless the practitioner or student will find in these pages a brief and satisfactory review of our present knowledge of the subject. A.

A CLINICAL GUIDE TO BEDSIDE EXAMINATION. By H. ELIAS, M.D., Dozent and Assistant at the First Medical Clinic of the University of Vienna, Austria; N. Jagic, M.D., Extraordinary Professor and Chief Physician to the Sofienspital, Vienna, Austria; and A. Luger, M.D., Dozent and Assistant at the Second Medical Clinic of the University of Vienna, Austria. Arranged and translated by WILLIAM A. BRAMS, M.D., Chicago, Ill., Adjunct in Medicine, Michael Reese Hospital. Pp. 135. New York City: Rebman Company, 1923.

THIS little book takes up physical examination of the patient systematically. It would be of value to hospital residents and medical students, during the last two years of their course, in teaching them how to make a thorough and complete physical examination. M.

HANDBOOK FOR MENTAL NURSES. Published under the authority of the Medico-Psychological Association. Seventh edition. Pp. 615; illustrated. Chicago: Chicago Medical Book Company, 1923.

THIS text-book, primarily for attendants in mental institutions, has much information for all nurses. While the major portion is devoted to the nervous system, its anatomy, physiology and nervous and mental disorders, the forepart of the book deals with nursing knowledge necessary for somatic disorders. The volume serves well its purpose. B.

THE OPHTHALMIC YEAR BOOK, 1923. Vol. XIX. Edited by EDWARD JACKSON and WILLIAM H. CRISP. Pp. 367. Chicago: The Ophthalmic Publishing Company, 1923.

THIS collaborated volume brings up the references to the current literature of ophthalmology through December, 1922. The chapter on Comparative Ophthalmology covers the period since 1916. Material is grouped under major headings with appropriate subdivisions, each chapter prefaced by a bibliography, following which the publications of individual workers are abstracted and summarized. The volume has been carefully edited and is an invaluable reference work for all students of ophthalmology.

I.

PRACTICAL MEDICINE SERIES. Vol. I. General Medicine. Series, 1923. Under the general editorial charge of CHARLES L. MIX, A.M., M.D. Pp. 678. Chicago: The Year Book Publishers, 1923.

THE volume on General Medicine of Practical Medicine Series for 1923 continues to follow the high standards set by the previous editions. One could hardly expect other than this when the list of editors is made up of such distinguished clinicians as Weaver, Lawrason Brown, Preble and Sippy and Ralph Brown. M.

METHODS IN MEDICINE: MEDICAL SERVICE OF GEORGE DOCK. By GEORGE R. HERRMANN, M.D., PH.D., Instructor in Medicine, University of Michigan; formerly House Officer, Peter Bent Brigham Hospital, Boston. Pp. 521; illustrated. St. Louis: C. V. Mosby Company, 1924.

THIS manual outlines in detail the various methods that are applied to the proper running of a medical service. The first section includes notes on the duties of a resident physician, assistant resident physician, the interns, record-room rules, roentgen-ray department rules, superintendent's rules and so on. The author then takes up the question of history-taking and physical examination and follows that with a long section on laboratory tests. Following this are sections on diets, succeeding which there is a portion of the book devoted to therapeutic methods and lastly apparently the whole series of charts that are used in the Barnes Hospital. In analyzing a book of this type it must be borne in mind that it has as its function the purpose of teaching the younger medical

man, more particularly the senior student and the junior intern. For that reason a large portion of it is of little value to the more mature clinician. However, the part that is of value to such an individual is of special value because it outlines to him various tests and laboratory procedures that might be difficult to find in the ordinary literature and difficult to remember from student days. To the reviewer there are two criticisms that seem pertinent. In the first place he believes that the section on history taking and physical examination is entirely too short and that the author could very easily incorporate a goodly portion of the "outlines of case-taking" by Doctor Dock in his Chapter VIII to the betterment of the work and he could do so by limiting the space devoted to the laboratory and chemical methods. Lastly, the reviewer hardly sees the necessity of placing on permanent record a large number of hospital charts, blanks and forms which occupy nearly a hundred pages of the book. With the exception of the above criticisms the book is first-class. It is a book teeming with practical points in the management of a hospital medical service and could be very well kept for reference in every hospital that does not have a technic book of its own. M.

GERIATRICS. By MALFORD W. THEWLIS, M.D., Editor, *Medical Review of Reviews;* Associate Editor, *The Therapeutic and Dietetic Age.* Second edition. Pp. 401; 24 illustrations. St. Louis: C. V. Mosby Company, 1924.

THE second edition of this book has been considerably revised and several new chapters added. The book is interesting, but one cannot help but feeling that it is rather hastily written in spite of the revisions, and that it does not go sufficiently deep or critically into the subject. For example, we doubt very much indeed if hepatic extract is of value in the treatment of liver disease and prostatic extract is of value in prostatic disease. M.

GESCHICHTE DER MEDIZIN. By PROF. DR. PAUL DIEPGEN, Honorary Professor of the History of Medicine in Freiburg. Second edition. Pp. 131. Berlin and Leipsic: Walter de Gruyter & Co., 1923.

IN the ten years since the appearance of the first edition of this work researches in medical history have made notable progress, especially in our knowledge of ancient medicine. These have been adequately treated in the new edition. The lives of individual preëminent physicians have been alluded to in greater detail. The book represents a brief, concise and withal illuminating presentation of the subject. K.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Cutaneous Hypersensitiveness in Enteric Infections with Special Reference to Enteric Carriers.—The recognition of enteric carriers frequently offers such difficulties that the suggestion given by McKENDRICK (*Jour. Path. and Bact.*, 1923, **26**, 535) for testing the suspected persons for cutaneous hypersensitivity to the typhoid group deserves earnest consideration. He investigated the following series of cases, using standard suspensions of the killed organisms: 5 chronic carriers, 14 cases of enteric fever, 19 persons who had undergone prophylactic inoculation and 2 with a previous history of infection; and in addition 360 control cases in none of whom was there history of enteric fever or prophylactic inoculation. Positive reactions were uniformly obtained in patients with enteric fever (up to the beginning of convalescence) and in chronic carriers. The tests seem to be highly specific since only suspensions of the type of organisms demonstrated in the feces would give positive skin reactions. Only 2 out of 360 control cases gave positive reactions, while all patients having had previous inoculation or the infection itself reacted negatively. One patient, while apparently convalescent from typhoid, continued to react positively; it is interesting to note that this patient suffered two relapses. It is suggested that all patients convalescing from enteric fever be examined for the skin reaction in addition to stool examinations, as the latter may often fail to aid in detecting carriers.

The Prevalence and Trend of Drug Addiction in the United States and Factors Influencing it.—KOLB and DU MEZ (*Public Health Reports*, 1924, **39**, 1179) have made an extensive study of the number of drug addicts that are present in the United States at the present time. From their statistics they hold that there are approximately 150,000 as a maximum

estimate, but they believe that 110,000 is a number more nearly correct. The addicts have steadily decreased since 1900 so that at the present time there has been a decrease of over 50 per cent, and this in spite of the fact that there are a large number of addicts in prison, more than there were twenty-five years ago, due to the more thorough enforcement of the laws of the country in respect to the use of opiates. The average daily addiction dose of morphin sulphate, heroin hydrochlorid and cocain hydrochlorid is not less than six grains. The use of opium and laudanum has been almost entirely abolished while cocain hydrochlorid is used only in conjunction with opiates excepting in a rare case. The actual known quantity of narcotics imported by the United States at the present time is only slightly in excess of that required to supply medicinal needs. While these figures are, of course, authentic, it does not by any means include the large quantities of these drugs which presumably are smuggled into the country. One pleasant feature of their study was the fact that doctors who had been so frequently incriminated as causing drug habit in patients, actually are responsible for only a very few cases and not all these can be substantiated. There can be no question that patients are in the habit of blaming physicians rather than their own inherent weakness when their sole purpose is to secure sympathy for their vice. The authors feel that as a result of the attention given to the problem by the medical profession and law enforcing officers that not many years distant the few remaining addicts will be persons taking opium because of an incurable disease and addicts of the psychopathic type who spend a great part of their time in prison.

The Pathogenesis of Primary Pneumococcal Peritonitis.—In a previous paper, McCartney and Fraser, (*Brit. Jour. of Surg.*, 1922, **9**, 479) clinical evidence was brought forth that primary pneumococcal peritonitis occurs only in females, mainly between the ages of two and eleven years. Of 56 cases of pneumococcal peritonitis studied by them, 36 were primary and 20 secondary. All of the 36 primary cases occurred in girls from two to eleven years old. Of the secondary cases, 12 were in boys and 8 in girls. The symptoms of the primary form were always first those of pelvic inflammation, and early operation disclosed only the pelvic peritoneum involved, frequently localized in the region near the opening of the Fallopian tubes. In the present paper McCartney (*Jour. Path. and Bact.*, 1923, **26**, 507) reports his studies on 10 primary cases (girls three and a quarter to six and a half years old). In all the cases the same type organism was cultured from the vagina as from the blood and peritoneal cavity. Only 6 of the 10 gave positive throat cultures, 1 of which was of Type IV, while Type I was found in the peritoneal cavity, blood and vagina. The vaginal flora of 150 children of the poorer class (to which class this form of peritonitis is nearly always limited) was studied over a period of one and a half years. Pneumococci could frequently be isolated, usually non-pathogenic Type IV strains, but on several occasions Type I was found. Pneumococci could not be demonstrated in the vaginal secretions of well-cared-for children. Vaginitis with an alkaline secretion, so often present among children of the poorer classes in the summer seems to favor the pneumococcal infection. Experimental production of the disease was successful only in the young female monkey. Here one of three

monkeys developed the typical pelvic peritonitis following inoculation of Type II pneumococcus broth into the vagina. The inflammation was most severe in the pelvis although the uterus and tubes presented nothing abnormal. The original culture was recovered from the peritoneal cavity and from the Fallopian tubes. The conclusion is reached that primary pneumococcal peritonitis is caused by an ascending infection coming from the vagina.

Roentgen-Ray Intoxication.—In a series of interesting papers, WARREN and WHIPPLE (*Jour. Exper. Med.*, 1924, **38**, 713) set forth the effects produced in animals by roentgen-ray destruction of the intestinal epithelium. Contrary to the prevailing idea that this epithelium is the barrier excluding intestinal bacteria from entrance into the blood stream, these authors find that its complete destruction does not lead to any bacterial invasion, until just preceding death. A profuse excretion of fluid into the intestinal lumen with vomiting and diarrhea accompanies the desquamation, however, so that this outflowing current may be one factor preventing such invasion. The conditions might possibly be quite different if active absorption could be induced along with the desquamation. The sensitivity of the intestinal epithelium to the rays should always be considered in treatment of abdominal or pelvic condition by radiation according to the authors. Intestinal lesions may be produced which may be repaired completely or may go on to form permanent ulcers. They were able to produce in animals ulcers which resisted healing as do peptic, duodenal, and other chronic intestinal ulcers. The small intestinal mucosa was found to be much more sensitive to injury than that of the stomach or colon.

SURGERY

UNDER THE CHARGE OF

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Chronic Vesical Distention.—SHAW and YOUNG (*Jour. Urol.*, 1924, **11**, 373) say that immediate and continuous bladder drainage is followed by a more or less severe reaction in the majority of cases of chronic urinary obstructions. The reaction may be predominantly renal, circulatory or nervous, but, usually there are symptoms referable to all three systems. The reaction in the urinary tract is the most constant and is shown by bleeding from the bladder and kidneys, the appearance of albumin and casts in the urine, and frequently an abrupt fall in the renal function as shown by the phthalein test and blood

chemistry studies. All these symptoms may be present without any change in the blood-pressure. Sudden reduction of increased vesical tension, renders the kidneys more susceptible to infection. The reaction in the circulatory system occurs less frequently but may be quite severe. Complete suppression of urine occurs as a result of the lowered blood-pressure. The present study does not show that the blood-pressure is regularly increased in prostatic hypertrophy, even when accompanied by marked chronic vesical distention. Mild nervous and mental symptoms, frequently follow sudden drainage of the overdistended bladder. These symptoms may occur without any changes in the blood chemistry. By gradually reducing the bladder pressure, the reaction can be avoided in most cases.

The Causes and Changes in Loose Bodies Arising from the Articular Surface of the Joint.—PHEMISTER (*Jour. Bone and Joint Surg.*, 1924, **6**, 278) says that the lesion does not seem to be a complete intra-articular fracture. Nutritional disturbance in the partially detached portion would favor the occurrence of non-union. Primary necrosis of the portion which becomes detached has been shown not to occur in at least a certain percentage of cases. After the body becomes loosened, degenerative and regenerative changes go on in it, both while it is attached by a pedicle and after it is completely liberated in the joint.

Mechanism of the Normal and of the Flat Foot.—MORTON (*Jour. Bone and Joint Surg.*, 1924, **6**, 368) says that flatfoot is essentially and primarily a faulty posture of the os calcis, by which an improper distribution of body weight and muscle force is transmitted to the fore part of the foot through its two channels, the scaphoid and cuboid bones. In the fore part of the foot, functional derangement is purely secondary to the improper distribution of forces thrown upon it from the posterior half. There is a loss of the normal balance of the forces passing through the foot, so that the unbalanced structure is caused to roll inward (pronate). The plantar ligaments are the only real weight supporting soft structures of the foot. The lateral muscles and ligaments are merely controlling in their actions and incapable of sustaining any considerable amount of body weight. The early movement of the faulty posture is almost directly lateral; the resulting progressive slant, however, of the calcaneal facets causes an inward shifting of body weight and the creation of a strong lateral thrust, which together constitute an overpowering burden upon the relatively weak lateral structures. This burden is termed a "false load," because it is a new and abnormal element of strain thrown upon lateral structures and by them is merely transmitted back again upon the leg and foot. Bone changes ultimately occur, which accord with the disordered movements of force and the uneven contact of joint surfaces.

The Renal Circulation.—LEE-BROWN (*Arch. Surg.*, 1924, **8**, 831) says that the coarse distribution of the renal vessels conforms to the generally accepted teaching. The atrophic or aborted glomeruli are found in close proximity to the medulla and represent glomeruli devoid of a capsule and whose specific function has ceased. The arterial rectæ originate as efferent vessels from glomeruli situated chiefly in

close relationship with the medulla. These vessels form the chief blood supply of the medulla. There are four distinct types of efferent vessels, subcapsular, cortical, cortico-medullary and medullary. All branches of the renal artery are not true end arteries, as a return flow may be obtained by way of the posterior division when the organ is irrigated with physiologic sodium chlorid solution through the anterior division of the artery. The renal circulation is irreversible. All findings have been actually observed and are individually substantiated by direct photographs.

Some Problems of Jaundice and Their Significance in Surgery.—De Takats (*Ann. Surg.*, 1924, **79**, 662) says two groups of jaundice can be distinguished that are best called cholemia and bilirubinemia. The first is caused by any disturbance in the bileflow, or by the incompetency of the hepatic cell; the latter is an overproduction of bilirubin, in consequence of an increased degree of hemolysis. The intact liver function is of high importance for the surgeon. Its disturbance will produce longer bleeding and coagulation time, a greater susceptibility for narcotics and a marked acidosis after the operation. In consideration of the imminent dangers of cholemia, these patients should be submitted to operation as soon as possible. Jaundice of hemolytic origin can be cured by splenectomy, although one might not always succeed in healing the actual disease. In cases of thrombopenia, the hemorrhage ceases after splenectomy, although the increase of blood platelets is only temporary.

Duodenal Ulcer Among Medical Men: A Comparison of the Results of Surgical and Medical Treatment.—Forsyth (*Brit. Med. Jour.*, 1924, **1**, 780) says there was no mortality in non-operated cases. Two of 3 deaths in operated cases, immediately followed operation. The absence of deaths among the non-operated cases is noteworthy, seeing that hemorrhage is noted fairly often. The special value of these figures, extracted from the registers of the Medical Sickness Society, is that they represent a business, and therefore impartial record of the after histories of the cases. They show that duodenal ulceration entails long periods of sickness and though not often mortal, is very liable to recur, even after many years; but the majority of cases recover after one attack and remain free from relapses. The figures give no support to the claims of greater effectiveness for either surgical or medical treatment, on the contrary they show that the results of the two methods leave little to choose between them.

The Effects of Chronic Irritations on the Morphology of the Peritoneal Mesothelium.—Cunningham (*Johns Hopkins Hosp. Bull.*, 1924, **35**, 111) says that it has been found that the injection of laked or whole blood or any other mildly irritating substance into the peritoneal cavity, causes the serosal cells to increase in number and at the same time to round up, becoming at first cuboidal and finally columnar. When desquamation occurs, the remaining serosal cells proliferate rapidly and cover over the denuded area. The change may progress until the layer of mesothelium is several cells thick, and even in this state it is ample to prevent the development of adhesions. In long

continued irritations, connective tissue proliferation takes place and small outgrowths appear in the parenchymatous organs, but even here the changed mesothelium rapidly covers the advancing core of blood-vessels and connective-tissue stroma preventing the development of adhesions.

Diagnosis and Treatment of Syphilis.—KILDUFFE (*Am. Jour. Syph.*, 1924, **8**, 142) states that diagnosis is essentially dependent upon the observation of certain phenomena in the patient, the recollection or knowledge that similar phenomena are associated with certain pathological entities and the correlation of the information thus obtained in terms of the patient. While it is admitted that the only venereal history of value is a positive one; nevertheless, careful history taking has produced many hidden but important leads. Stokes and Brown found that 70 per cent of syphilitics with gastric complaints had neurosyphilis and what is of greater practical importance 60 per cent of their series had had no recognizable secondaries. Standard courses of treatment of all kinds abound in spite of the fact that there is and can be no true standard under all circumstances. The essence of the problem is perseverance and persistance, which alone spell safety. The so-called "Wassermann-fast" cases in the opinion of Stokes and Busman should not be dismissed from careful search for evidence of activity at intervals throughout life, for they are potentially syphilitic and show a high incidence of cardiovascular syphilis. These cases can be made negative by persistence and at times varied treatment.

THERAPEUTICS

UNDER THE CHARGE OF

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The Action of Physostigmin and Pituitrin: The Action of These Drugs Alone and Combined upon the Isolated Human Vermiform Appendix; the Advantages of Their Combined Use in Postoperative Ileus.—KERR CROSS (*Brit. Med. Jour.*, January, 1924, p. 9) record the satisfactory results obtained by the subcutaneous injection of physostigmin, gr. $\frac{1}{100}$, and pituitrin, gr. $\frac{1}{2}$, for relief of dynamic ileus. Professor Gunn first pointed out the synergism between pituitrin and physostigmin from his work on laboratory animals, and this finding was confirmed by the author by his experiments on the human vermiform appendix. Neither drug alone produced much effect; but the drugs in combination caused a marked muscular contraction of the appendix. A number of cases of severe postoperative atony are described in which this combination relieved the condition when either drug alone failed to do so. No case treated has failed to be relieved unless there was unsuspected mechanical obstruction.

Addison's (Pernicious) Anemia and Subacute Combined Degeneration of the Spinal Cord.—In 1889 Hunter suggested for the first time that Addison's anemia is due to excessive destruction of blood caused by the absorption of hemolytic poisons from the alimentary tract. HURST (*Brit. Med. Jour.*, January, 1924, p. 93) believes that a definite infection of the intestine with a hemolytic streptococcus is present in Addison's anemia. In every one of the 10 cases of Addison's anemia and the 5 cases of subacute combined degeneration of the cord which were investigated the Streptococcus longus was found on cultivation of the duodenal contents. In normal individuals and in patients suffering from other conditions it was cultivated in only 10.9 per cent of cases. He believes that achlorhydria is an essential predisposing cause of Addison's anemia and its associated subacute combined degeneration of the cord because there is a loss of the normal antiseptic action of the gastric juice which makes it possible for the streptococci from the mouth to reach and infect the intestine. There is nothing specific about the achlorhydria, and it is in most cases caused by constitutional and congenital absence of gastric juice—achylia gastrica—in which no hydrochloric acid and very little or no pepsin are secreted, but it may also be caused by acquired achylia and by any condition in which such acid as is secreted is at once completely neutralized. The most important part of the treatment of these conditions consists in overcoming the intestinal infection and arresting the development of neurotoxic and hemolytic poisons. Oral sepsis should be eliminated, also infected tonsils, and infection of the sinuses corrected. The achlorhydria should be treated with large doses of dilute hydrochloric acid to each dram of which 1 gr. of pepsin is added. Six drams of dilute hydrochloric acid should be mixed with $1\frac{1}{2}$ pints of water to which sugar and the juice of three oranges or two oranges and one lemon are added. One-third of this amount is taken before and during meals. As the achlorhydria remains permanently in most cases this acid mixture should be taken for the rest of life without intermission. Milk which has been soured with an active lactic acid bacillus should be taken between meals in an attempt to check the growth of pathogenic bacteria in the intestine. Charcoal is also given in tablespoonful doses night and morning to absorb gas and correct flatulence. Autogenous hemolytic streptococcic vaccine made from bacteria obtained from the duodenum, teeth, or tonsils should be given over a long period of time and in doses so regulated as not to give rise to any general reaction. Splenectomy gave good results in 2 of his cases of anemia and by removing one source of blood destruction is a rational but not universally successful procedure. Symptomatic treatment should always be given, and arsenic and direct transfusion of blood are both of benefit. The latter may not only raise the percentage of hemoglobin, but frequently initiates a steady rise in the percentage.

The Principles of Treatment of Gastric Ulcer in View of Recent Work.—BOLTON (*Brit. Med. Jour.*, January, 1924, p. 139) states that the majority of gastric ulcers will heal if the normal responses of the stomach to the stimulus of food can be restored and maintained. He believes that the ulcer acts as an irritant and effects the neuromuscular mechanism of the stomach, the acidity of the gastric contents, and the

amount of gastric juice secreted. Irritability of the pyloric sphincter prevents normal relaxation and delay in the emptying of the stomach results. Because of the delay in the emptying of the stomach the percentage of free and combined HCl rises above the normal 0.2, at which point the pylorus should relax to allow regurgitation of bile and pancreatic juice. The result is that the HCl continues to rise, due to the prolongation of the digestive process which causes hypersecretion of the gastric juice. The treatment consists in an attempt to restore the normal gastric functions, that is, to lessen the neuromuscular irritability of the stomach and facilitate the emptying of the organ, and to restore the normal degree of duodenal regurgitation and to reduce the amount of gastric juice secreted. Preliminary treatment lasts six weeks, during which time the patient is put to bed to reduce expenditure of energy, the desire for food, and the work of the stomach. Gradually the diet is increased until the patient is eating the full diet to be allowed, and then he gets up and proceeds to the subsequent treatment, during which he eats the full diet he is to be allowed. At first the diet consists of the following foods presented in the following order: Milk, raw eggs, thin bread and butter, boiled eggs, cereals boiled in milk, pounded fish or chicken, mashed potato, sieved green vegetables, ordinary fish, chicken and mutton. Meat extracts are not given at all, nor meats nor other foods which are not easily disintegrated. Beginning with 7 ounces of milk every three hours from 7 A.M. to 10 P.M., the diet is gradually enlarged with substitution of the foods listed above, and eventually three meals a day are given. Alkalis are given one and a half to two hours after each meal and also once or twice during the night if the patient is awake. The best alkalis to administer are bismuth subcarbonate, calcium carbonate, magnesium oxide and soda bicarbonate. Atropin also has its uses particularly in relaxing the pyloric sphincter. The only direct means of dealing with a chronic ulcer is to excise it. Otherwise the aim of surgery is precisely the same as that of medicine, namely, (1) to facilitate the emptying of the stomach, and (2) to induce the regurgitation of intestinal fluids into the stomach. The writer believes that intestinal feeding should only be used in cases of bleeding from the stomach and in uncontrollable vomiting.

The Management of High Blood-pressure. — (*Therap. d. Gegenw.*, 1923, **12**, 437) divides the cases of arterial hypertension into: (1) The acute arterial spasm with increased pressure; (2) the chronic hypertension, due to a hypertonic condition of the muscle cells of the arterial wall. The former are comparatively easy to influence, while the latter are very difficult. Baths, warm packs, light-baths, diathermy and also cutaneous irritants, such as the faradic current, may correct the former. Drugs which are effective are papaverin benzol compounds, such as benzol-benzoate and benzalcohol and particularly akineton, which is soluble in water and can be used intravenously in large doses. Papaverin, 0.08 gm., should be given in cases of arterial spasm. Spirits of camphor, 20 to 30 drops, often give good results; also extract of the anterior pituitary. The nitrites are also active, but their action, like many other substances becomes neutralized easily. Chloral hydrate also is an effective depressing agent, but in cases where the heart

muscle is good it often keeps up the effect of the irritating agent. The cases of chronic hypertension should be observed to determine their normal pressure, and the excess pressure corrected by means of vacations, rest, change of climate, avoidance of excitement, and avoidance of overweight. Diminution of salt intake in uncomplicated cases is of no benefit. Lukewarm baths and CO_2 baths are also of benefit. Drugs are useful in lowering the excess pressure only, but he also considers that it is important to give a diuretic weekly, or twice a week. Except in luetic cases he does not consider iodids of benefit, but often gives sodium rhodanate 1 to 3 gm. per day. He believed the dangers of permanent high blood-pressure are overestimated. The condition of varying pressure is serious, and the prognosis is unfavorable in those cases which show cerebral, renal or pancreatic symptoms.

PEDIATRICS

UNDER THE CHARGE OF

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Hypernephroma of the Ovary. Report of Case.—DOWNES and KNOX (*Jour. Am. Med. Assn.*, 1924, **82**, 1315) report a case of this character of which only 11 cases are to be found in the literature. Only one of these other than the case herein reported began active growth in infancy and exerted the fundamental influences on growth and sexual development which such a tumor may do if active during the formative period of the individual. These 2 cases showed premature sexual development, a phenomenon that may result occasionally from disturbed ovarian function associated with a cyst or sarcoma of the gland, though it is by no means a constant finding with ovarian tumors in infants, as its frequent absence contributes to the difficulties of diagnosis. Suprarenal tumors composed of pigmented cortical cells arising in infants and in young children regularly cause striking developmental changes, while sarcoma and lymphosarcoma do not necessarily do so. In such a case as the one reported here, the effect is probably due more to the tumor cell type rather than to the secondary effects on the ovary, but it is impossible to separate these two factors completely, either normally or pathologically. Pure suprarenal types usually show a precocious growth of body and sex organs, overgrowth of hair and of fat, pigmentation and frequently mental dulness. Many patients have shown a tendency toward a masculine type. Precocious menstruation has only been noted once in the suprarenal group, and that was after the tenth year. Nearly all of these patients have died in childhood, either because of their glandular dyscrasia has rendered them very susceptible to intercurrent infections, or more often because the tumors, being large, inaccessible and frequently metastasizing at the time of operation, have caused the patient to succumb at the time of the

operation. The ovarian cases, with readily accessible benign growths have been frequently greatly improved by operation, and a recession of the pathological characters has occurred. The interrelation of the endocrine glands is undoubtedly very important, most of the symptoms are due to imbalance of the secretions.

Congenital Mitral Stenosis.—DONNALLY (*Jour. Am. Med. Assn.*, 1924, **82**, 1318) reports a case that died at the end of fifty-seven hours. This is the twelfth case in the literature in which autopsy findings definitely established the diagnosis. He says that the explanation of this anomaly is comparatively simple. The defect happened during the differentiation of the mitral valve out of the endocardial cushions. The free margin of these cushions grow down into the ventricles, and the muscular trabeculæ from the heart walls invade their structure, and form their attachments so that for a time the valve consists partly of endothelial growths and partly of musculature. A differentiation into musculi papillares, chordæ tendinæ and valve flaps develops as the musculature in these structures degenerates. This is the point at which something happens in congenital stenosis to prevent the normal development into valve segments. Growth is arrested in the mitral valve and in those chambers and vessels whose growth is dependent on the proper functioning of the left auriculoventricular orifice, particularly the left ventricle, aorta and left auricle. The completion of the subdivision of the heart, the almost complete development of the valve apparatus, and the outer form of the heart occur by the time the embryo is eight weeks old. With the establishment of the narrowed left auriculoventricular passage, arrest in development of the left heart ensues because of the small amount of blood that is permitted to take the normal through it, while there is dilatation and hypertrophy of the right heart because of the amount of blood that it receives and propels. As the intraventricular septum was completely formed and closed in this case, blood entered the left ventricle solely through the stenosed mitral orifice, but in such small volume that this ventricle had almost no function to perform and remained undeveloped. The left auricle, receiving the blood from the lungs and unable to send it into the left ventricle, may have passed it through the foramen ovale into the right auricle. It is difficult to say that this was definitely the case, although the large and comparatively powerful right ventricle may have made its force felt through the pulmonary circulation and have been an added factor to left auricular contraction to produce this result. In the literature, the children with the greatest duration of life showed a closed foramen ovale. This indicates that patency of the formane ovale is not of great compensatory value. In this case almost the entire function of the heart was performed by the right side. As a result, there was an enlarged right ventricle and dilated pulmonary artery. Persistence of the ductus arteriosus permitted the passage of blood through the aorta in a reverse to the normal direction into the vessels of the head and upper extremities and onward into the thoracic aorta.

Wilson's Disease in Infancy.—PAUL (*Arch. f. Kinderh.*, 1924, **74**, 38) reports a case of an infant with tonic spasm, jaundice, normal color of feces, and much enlarged liver, but absolutely normal spleen. He

diagnosed this as Wilson's disease, which is an extrapyramidal symptom-complex, concomitant liver cirrhosis and lenticular degeneration. Banti's and Gaucher's disease and syphilis could be positively excluded. Since the pallidum symptoms harmonized with the second type of Little's disease, the case might be diagnosed as Little's disease as well. Along with the typical pallidum symptoms, dorsal flexion of the foot, crossing of the legs, flexion of the knees, dropping position of the hands, increased surface tonicity of the muscles and non-decreasing muscle rigor during passive motions there occurred one striatal symptom, opisthotonos.

Further Notes on the Treatment of Pertussis by the Roentgen-Ray. —Bowditch (*Jour. Am. Med. Assn.*, 1924, **82**, 1422) presents the results of treating 300 cases of pertussis by the roentgen-ray. Patients were given treatments every alternate day for three treatments. After an interval of seven days, a similar second course of treatments was given in the more protracted and resistant cases. These additional treatments were infrequent, as they did not as a rule seem necessary. The ordinary dosage for a child of from five to ten years was five minutes exposure with the tube set at 4 ma.; a 1 mm. aluminum filter and a 6- to 7-inch back-up-spark at a distance of 28 inches, was employed. This dosage was gradually graded down somewhat, according to the age of the patient, so that an infant of three or four months would receive the same dosage, with the exception of the time interval which would be three instead of five minutes. The first treatment was given over the anterior chest, the second over the back of the chest, and the remaining treatments alternating in this manner, the total dosage was well within the limits of safety, four exposures totaling less than one-half an erythema dose. In case the symptoms persisted a second series of treatments of the same dosage was given after an interval of ten days to two weeks. This happened rarely. Very few of the patients had more than four treatments. The clinical course of the disease seemed to be definitely modified. Within a few hours after the first treatment, the patient experienced a feeling of relief. The symptoms were reduced in severity and duration. At the end of twenty-four hours, the symptoms usually reverted to their former degree, and the next day no very marked effects of the treatment was noted. After the second treatment, the symptoms usually fell back a little. There were some cases in which the severity of the paroxysms was less after the first treatment. The most marked changes followed the third treatment. The patient seemed more noticeably relieved as the severity of the paroxysm was reduced, whooping almost disappeared, cyanosis and vomiting became minor factors, and often more uninterrrupted sleep at night followed. By the end of the week, the appetite usually improved, and the patient was much better. While these results do not always follow, in general the earlier the case is treated, and the younger the patient the better is the response. Extremes were encountered. Sometime the mother reported a cure as the result of one treatment. Other cases persisted with no very marked benefit in spite of the two courses of treatments. In the entire series of cases, including 100 children under two years of age, only 1 death occurred.

Meningitis: Distribution According to Age and Etiology.—Neal (*Jour. Am. Med. Assn.*, 1924, **82**, 1429) analyses 1523 cases. She found that with the exception of tuberculous meningitis more cases of meningitis occur in the first year of life than in any other one year. The number of cases of meningococcic meningitis in the first year exceeds by far those in any other year. The greatest number of cases of tuberculous meningitis is found in the second year of life. In times when there is no epidemic, the number of cases of tuberculous meningitis exceeds or at least equals the number of cases of mengococcic meningitis. After the meningococcus, the pneumococcus and the streptococcus are the most common causes of purulent meningitis, followed by the influenza bacillus, the straphylococcus and Bacillus coli group, in the order named. Cases due to the last two organisms are comparatively rare. Other pyogenic organisms occasionally cause a meningitis, and more rarely, members of the higher group of organisms such as members of the streptothrix and the pathogenic yeasts are the causes. Mixed infections are rare.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Pathogenesis of Arsphenamin Death.—Kritschewsky (*Arch. f. Dermat. u. Syph.*, 1923, **144**, 32, 47) and Kritschewsky and Friede (*Ibid.*, p. 61) discuss at some length in connection with experimental studies the pathogenesis of arsphenamin death. In his introduction, Kritschewsky calls attention to the arsphenamin mortality of 16 per 100,000 in the German empire from 1909 to 1914, and the fact that this mortality would reach 514 per 100,000—5 per 1000 patients—if the accidents indirectly attributable to arsphenamin were included. He reviews in some detail the various conceptions of acute arsphenamin death, including the conceptions of water-error from the endotoxins of bacterial contamination, Herxheimer flare-up in secondary syphilis, the anaphylactoid manifestations of nitritoid crisis, and the later complications including especially the cerebral manifestations of hemorrhagic encephalitis. He includes in this group several cases with prolonged "incubation periods" ranging from six weeks to three months, which must seem somewhat apocryphal to us. Kritschewsky employed in his investigation the determination of the effect of injected arsphenamin solutions upon the complement content of guinea-pig serum as an evidence of changes in its colloidal dispersion following the administration of the drug. This method has been made the subject of previous study by this author and was regarded as a reliable index to colloidal change. He found that *in vitro* definite reduction or fixation of complement occurred following the administration of arsphenamin

as indicated by a hemolytic system. This physico-chemical change took place although no visible precipitate appeared in the blood serum such as is known to form with acid arsphenamin. He then transferred his experiments to animals and demonstrated that similar changes occurred in the rabbit and mouse indicating an alteration in the dispersion of the serum even by properly alkalinized arsphenamin solution. The effects of this physical change were manifested in the occurrence of intravascular coagulation with agglutination of red blood cells which in accord with observations of Oliver and his co-workers previously reviewed. Kritschewsky believes that the mechanism by which this colloidal dispersion is produced is identical with that producing the dispersion changes of anaphylactic shock. In this respect he differs with the views of certain American investigators who do not believe that acute arsphenamin intoxication should be regarded as anaphylactic in character. In collaboration with Friede, Kritschewsky carried his experiments further, studying the pathological changes produced by acute arsphenamin death. These confirm in large measure the findings of previous investigators with reference to the role of wholesale intravascular thrombus formation. The tremendous pathological change occurring in the tissues is of the type which one would expect with disturbance of their colloidal equilibrium, including liquefaction of muscle tissue and confirms his opinion that colloidal changes form the ultimate basis of the damage done by arsphenamin to tissue. In further experimental studies he was able to demonstrate the neutralizing or buffering power of serum against toxic arsphenamin; results which are also in accord with the work of Oliver and his collaborators on colloid (gelatin) buffering of arsphenamin solution. Kritschewsky finds in agreement with Gennerich and other authors that the concentration of the arsphenamin solution is one of the most potent factors in determining its effect upon the body colloids and the toxic reactions which it produces. Arsphenamin given in high concentration is much more dangerous than when well diluted.

Familial Dermatosis.—Thompson (*Brit. Jour. Dermat. and Syph.*, December, 1923, p. 455) describes a familial dermatosis of which he has been unable to find any account in the literature. Two girls in the same family were affected. The older child developed the condition at the age of one month in the form of a small red patch appearing on the most prominent part of each buttock. Similar lesions then developed in the face and gradually extended until both cheeks were greatly swollen, tense and highly polished and of a vermilion color. There was considerable underlying cyanosis and the hands were cyanosed and swollen though the feet were unaffected. Both buttocks showed changes similar to the cheeks. Marked improvement occurred under small doses of thyroid. The swelling and some of the color disappeared but a telangiectatic and nevoid condition persisted. At last report the process was extending steadily over the forearms and the extensor surfaces of the legs. The condition showed a predilection for the extensor surfaces. In the gross, the condition suggested greatly exaggerated *cutis marmorata*. The child was very suceptible to cold and the skin becomes purple at these times. The younger child was beginning to present the same manifestations as the older. Investigation

for syphilis so far as the Wassermann test is concerned was negative. The condition of the older child has persisted now for two years and the skin of the younger is just beginning to be affected at the age of three and a half months. At their very onset, the lesions were apparently follicular and had a nutmeg-grater feel. In the discussion erythroedema (pink disease) and angioma serpiginosum were considered but were apparently eliminated from the diagnosis. There were no systemic phenomena to suggest erythroedema. The same issue of the *British Journal of Dermatology and Syphilis* contains an excellent review from the *Medical Journal of Australia* of an article by E. Sidney Littlejohn, summarizing the symptomology of erythroedema or "pink disease."

Spinal Fluid in Syphilitics without Manifestations of Neurosyphilis.—M. PAPPENHEIM (Vienna) (*Arch. f. Dermat. u. Syph.*, 1923, **144**, 117) discusses the significance of the spinal fluid in patients with syphilis who show no manifestations of neurosyphilitic involvement. As a result of an extended review of the literature, he reaches the following very interesting conclusions: Increased pressure of the spinal fluid is without significance with reference to involvement of the nervous system in syphilis; isolated increases in albumen (positive globulin tests) are likewise not of unfavorable prognostic significance; syphilitic patients who in the stage of advanced latency show marked abnormalities in the spinal fluid may be regarded as proportionately seriously in danger of neurosyphilitic involvement. On the other hand, it is noteworthy that a considerable number presenting even severe changes do not later develop neurosyphilis. The immunity of women in this particular is pronounced. Statistical studies by Fuchs and Meyerbach make it seem very probable that not a few syphilitic patients in advanced latency have normal spinal fluids but none the less develop neurosyphilis. Pappenheim opposes the belief that later neurosyphilis is practically always the sequel of an early syphilitic meningitis. The changes in the spinal fluid in certain cases in advanced latency may be regarded as the sequels of parenchymatous involvement rather than its predecessors.

Cutaneous Sporotrichosis in the Rat.—JESSNER (*Arch. f. Dermat. u. Syph.*, 1913, **144**, 139). The author finds that cutaneous sporotrichosis in the rat because of its uniform incubation period and relatively long intervals between the disappearance of the traumatic inoculation crust and the beginning of manifestations of the disease, lends itself particularly well to the study of immunity of phenomena. The histological picture is very typical and consists of a connective-tissue reaction developing in the course of the existing immunity and expressing in a definite way the course of the developing immunity. Immunity reaction against cutaneous reinfection begins before the clinical manfestations of the first infection develop. The incubation period does not, therefore, represent as required by the von Pirquet and Schick theory, merely the time from inoculation to the beginning of the disease. It is necessary, therefore to distinguish in certain infectious diseases especially of the skin, as Neisser suggested in the case of syphilis, between a clinical and a biological incubation period. The latter is defined as

the time between the introduction of the exciting agent and the appearance of any detectable evidence of defense. The immunity incubation time is the period from the introduction of the exciting agent to the appearance of immunity against reinfection of the same agent. In sporotrichosis in rats the immunity incubation is shorter than the clinical incubation. The immunity against cutaneous infection appears later when the initial infection is subcutaneous than when it is cutaneous. The allergic response to subcutaneous reinfection is, in both subcutaneous and cutaneous initial infection, more pronounced at the site of previous inoculation than in sites not previously involved. This is of significance in the corymbose lesions of late syphilis and leishmaniosis in which the site of a previous involvement shows a markedly greater sensitiveness than previously uninvolved tissue. Jessner found evidence that tuberculoid histological structure is an allergic tissue reaction and appears at points where the infectious agent is being broken down under the influence of antibodies.

OBSTETRICS

UNDER THE CHARGE OF

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A Clinical Study in Hydrops Gravidarum.—SCHOEMAKER (*Arch. f. Gynäk.*, 1923, **119**, 305) has made a study of this condition, and finds that at the end of pregnancy 64 per cent of women show some sign of edema if the examination be made in the morning hours, and at evening 95 per cent of these same patients show edema in varying degree, and the lower extremities are markedly swollen in 11 per cent. In 200 pregnant patients general edema without pathological changes in the urine was observed only twice. In 3 per cent of the cases both morning and evening examination of pregnant women showed no edema. A slight edema at evening in pregnant women is without significance and does not prove that water is retained in the body because of pregnancy, because the same condition is observed in healthy women who are not pregnant. Marked edema is significant in the pregnant when it is attended by irregularity in weight and when in the puerperal period there is great increase in diuresis with also gain in weight above the normal. In general, in the last month of pregnancy 73 per cent of pregnant women show edema to some extent; this usually begins in the thirty-fourth week and becomes more marked as pregnancy advances. Swelling of the fingers is comparatively rare, occurring in 15 per cent of the cases, and usually denotes a marked pathological condition. When the diuresis of pregnant women is studied no marked difference can be detected between that of the night and that of the day. The concentration test is successful and significant in cases of edema of pregnancy and indicates that the

function of the kidneys is not especially disturbed. The rest nitrogen is below the normal in the urine in the most severe forms of edema. Blood-pressure is not, as a rule, altered in the mild forms of edema. Actual changes in the structure of the heart cannot in these cases be demonstrated. The fact that edema does not depend upon conditions in the kidneys suggests that in treatment rest in bed, diet free from salt and with a limited quantity of water is indicated. Where the condition is severe free sweating may be of service.

The Significance of Jaundice in Eclamptic Cases.—Oppenheimer (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, **5**, 289) describes the case of a primipara, aged nineteen years, with typical eclampsia; blood-pressure, 150; albumin and granular and hyaline casts in the urine. The patient was at once treated with narcotics by Stroganoff's method, including the use of chloroform. Delivery was effected by incising the partly dilated cervix and using forceps; the child was somewhat premature and to some degree asphyxiated. In the two days following labor the temperature rose to 102.5° F.; pulse, 150; there was cyanosis and dyspnea, and on the third day marked jaundice was present and the conjunctivæ were deeply colored. In the urine was biliary coloring matter and urobilinogen. Eclamptic convulsions recurred; Stroganoff's treatment of bleeding, injecting glucose and using chloroform, was continued. In addition to the jaundice there appeared reddened areas on the face, forehead, cheeks and upper portion of the thighs, which was diagnosed as toxic erythema. This gradually disappeared; three days later the temperature again rose and petechia developed; from this the patient became better and, after some disturbance in the stomach, she finally recovered. During this time the rest nitrogen in the blood was never increased nor was blood sugar. In the urine the albuminoid content was lessened and rapidly became less; casts disappeared, but urobilin and bilirubin and urobilinogen were present and diazo reaction could be obtained. Various tests for bilirubin in serum gave a marked increase without an especially increased diazo reaction. The leukocytes rose to 30,000; the hemoglobin was somewhat lessened followed by a rapid fall in the number of leukocytes and increase in hemoglobin. An acute toxemia developed in the first stage of labor, and it is interesting to note that convulsions returned three days after the delivery of the child. Such an occurrence is rare, but Olshausen has reported a case where convulsion reappeared seven days after labor in an eclamptic woman. The history of the patient gave no evidence of previous disease or infection of the liver, gallbladder or intestines. There was no history of poisoning by phosphorus or arsenic. Wassermann reaction was negative; examination of the blood for typhoid and paratyphoid was also negative. It was thought that the clinical picture was that of acute yellow atrophy of the liver; in that condition icterus appears at the very beginning or very early in the attack. In the case under consideration no diminution in the size of the liver could be detected; the writer considered the action of chloroform upon the liver and also that of chloral hydrate; before the appearance of the jaundice chloroform had been used for a considerable time, and the patient had been given 6.5 gm. of chloral

hydrate. On studying the clinical records it was found that jaundice may develop in cases where chloroform and chloral hydrate are not used; upon this ground the writer believes that these substances were not the cause of the jaundice. The writer believes that van den Bergh's method of estimating the bilirubin in the blood gives excellent grounds for estimating the gravity of the condition present in these cases. The prognosis in these patients is usually exceedingly bad; in the writer's experience in cases of icterus complicating eclampsia the mortality was 14.3 per cent, and if 6 very mild cases are removed from the category the mortality rises to 22 per cent. The mortality rate for eclampsia without icterus, he states, was 19.7 per cent. He is disposed then to revise the usual opinion that icterus developing in the course of eclampsia is not exceedingly deadly—an opinion which is very natural in a physician who has had a case followed by recovery.

The Post-mature Child.—O'KEEFE (*Am. Jour. Obst.*, November, 1923, p. 388) describes the difficulties seen in the delivery of post-mature children. There is a higher percentage of injuries to the mothers and higher mortality and morbidity among infants. The occiput was posterior more frequently than normal and rotates less readily spontaneously or by artificial means. There is greater difficulty in selecting the method of delivery, and the delivery itself is often difficult. The cause for the prolongation of pregnancy is not definitely known and in some instances it would seem as if the unusual growth of the child had something to do with it. There were 152 cases of children weighing 4000 gm. or more; of these 148 were white and 4 negroes. There were 144 pelves classified as normal, the others contracted or deformed. It is difficult to obtain an accurate menstrual history in these cases and, from the history itself, to compute accurately the intrauterine life of the child. There were 151 vertex presentations and 1 breech. Of the vertex presentations 31 had the occiput on the right side posteriorly, of which only 27 rotated spontaneously. There were 17 cases with occiput behind on the left side and of these 14 rotated spontaneously. The tendency to posterior position of the occiput increased directly with the weight of the child. The average length of labor was thirteen hours and nineteen minutes. In 82 cases morphin and scopolamin were used; pituitrin was given in 42 cases, varying from an injection of 1 ♏. to eleven injections averaging each 4 ♏. In 1 of these cases that had the largest number of pituitrin injections before birth the uterus relaxed immediately after delivery, and it was difficult to control the hemorrhage. Forty-one of the children breathed spontaneously; of these 1 died on the third day from pneumonia, another from intracranial birth injury. Labor had been induced in these cases, in the first with pituitrin alone and in the second with pituitrin and bougies. There were 5 abnormalities among these children; 5 injuries and 5 still-births. The 10 fatalities among the children gave an infant mortality of 6.5 per cent. The average weight was 4262.6 gm.; length 51.96 cm., with measurements corresponding. The writer considers the question of treatment by diet and the induction of labor.

GYNECOLOGY

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Indications for Myomectomy.—In recent years myomectomy seems to be regaining its old popularity in the treatment of certain types of uterine fibroids, and we have from time to time called attention to reports of fairly large series. Although the series reported by MILLER (*New Orleans Med. and Surg. Jour.*, 1924, **76**, 355) is not very large, it is carefully analyzed and may be of value to those interested in this subject. In 50 consecutive cases there was 1 fatality, a 2 per cent mortality, and of the 35 cases which he was able to follow up, there was only 1 recurrence (2.8 per cent). Following the operation 95 per cent of the patients menstruated normally and 97 per cent of the cases report their general health markedly improved. Five per cent of the patients report menstruation still profuse, though in practically all of the cases the flow is distinctly less. Dysmenorrhea is very commonly associated with fibroids, and a large number report this symptom either improved or more readily controlled by simple measures. Two patients have not menstruated since the operation; one of these was forty-eight years of age, and the myomectomy was done in the course of very extensive work in the upper abdomen; the other patient was thirty-six years of age. The conclusion to be drawn is that about 5 per cent of the cases will continue to menstruate profusely following myomectomy. Nevertheless, since we have an ideal therapeutic agent in radium, which can be used in graduated doses without producing a premature menopause, this objection is also not insuperable. The next important point to be considered is what percentage of women bear children after this operation. So many considerations enter into this however, that no definite conclusions could be drawn without an exhaustive study of a large series of cases. In this series, among the 35 patients who were followed, 6 were unmarried, and there were 10 pregnancies among the remaining 29 patients (about 28.6 per cent). Of these, 6 patients (60 per cent), had not been pregnant previously. Of the 19 who had the chance of pregnancy and did not conceive, it is interesting to note that 14, or over 75 per cent had been married prior to the operation sufficiently long to have borne children, and yet had never been pregnant. The average woman desires to preserve the menstrual function and to become pregnant if she can, and myomectomy makes both of these things possible, while pregnancy follows in a sufficient number of cases to recommend the operation unqualifiedly whenever it is indicated. Some women will insist upon the assurance that hysterectomy gives, that there will

be no return of the trouble, and request that that type of operation be done which will make the outcome final. However, if the advantages of myomectomy are placed before the average woman, and if the possibility of the use of radium if the trouble does recur is explained to her, she will usually prefer myomectomy when it can be performed. In deciding whether hysterectomy, myomectomy or radium is indicated in uterine fibroids, we must taken into consideration not only the number, size and location of the fibroids, but also the age, social and financial condition of the patient. When a woman is dependent on her own efforts, and perhaps is supporting a family also, when it is imperative that she return to work at the earliest possible moment and in the best possible condition, no chance must be taken of a second operation or even further treatment. Myomectomy has few indications after the age of thirty-eight, and in this series 86 per cent of the cases were under this age. When a woman has several living children there is less reason to preserve the uterus than in the case of the woman with no children who particularly desires motherhood. It is well to preserve the uterus if possible when there is an associated prolapse, as an interposition operation can be done with satisfactory results and with no danger of a subsequent prolapse of the vaginal walls. Neither radium nor myomectomy have the slightest indication when there is associated disease of the appendages. In brief, the ideal case for myomectomy is the single, well-defined encapsulated tumor. As a rule, the case presenting numerous small growths does not give satisfactory results. It is easy to overlook them, and if they are of different types and widely distributed, a damaged and useless organ may be left and the whole point of the operation be defeated. The author has, however, removed as many as 18 growths from one uterus, the woman afterward conceiving and delivering normally, and in 28 of the 50 cases in this series multiple growths were removed, some of them from five to eight inches in diameter.

Gonorrheal Complement-fixation Test in Women.—As a result of their work with the complement-fixation test in the diagnosis of many women afflicted with gonorrhea, most of whom were prostitutes, BARRINGER and VON BOSE (*N. Y. State Jour. Med.*, 1924, **24**, 10) have concluded that they are willing to make a definite diagnosis of gonorrhea on a "plus or minus" reaction, which they consider a weakly positive reaction, as they are satisfied that a non-gonorrheic does not give a positive reaction. In women the test has a distinct value, which is greatest in the chronic and subacute cases, from the standpoint of diagnosis and prognosis. It is of less value in acute cases, from the standpoint of diagnosis, but probably of equal value from the standpoint of prognosis. This study has proven the subsidence of the complement-fixation reaction along with the clinical symptoms, while the reappearance of a high complement-fixation reaction during convalescence suggests an active focus. A persistently negative complement-fixation reaction with positive bacteriological findings is rare and cannot be satisfactorily explained by these observers, but a persistently negative test with negative clinical and bacteriological findings can be interpreted as an index of the probability of a cure of gonorrhea in women. It is always a difficult matter to state just when a woman has been

cured of gonorrhea but these investigators suggest as a tentative and entirely standard that, in order to pronounce a cure, it is necessary to have three persistent negative findings over a period of six months. They fix this arbitrary time as they believe the cure in women is probably somewhat slower than in men.

Operation for Uterine Prolapse.—In describing his new operation for uterine prolapse, GILL (*Med. Jour. Australia*, 1924, **1**, 37) claims that it is suitable for use in all forms of extreme prolapse in women past the child-bearing period, provided that the uterus be healthy enough to be preserved and irrespective of the size of the organ. The abdomen is opened in the midline, the uterus drawn out and the tubes and ovarian vessels are clamped, divided and tied. The broad ligaments are opened by blunt dissection and the uterine arteries are picked up and tied. The uterus is then replaced in the abdomen with the anterior surface exposed. From this surface two flaps 4.25 cm. long and 2.5 cm. wide and 0.6 cm. thick are raised, the attachment along their mesial borders being retained. The uterine cavity is not opened. While the flaps are protruding through the wound the peritoneum and aponeurosis are closed by continuous sutures of catgut around the flaps. The uterine flaps are then laid flat on the aponeurosis and sutured to it by interrupted sutures of catgut. In spite of ligating both ovarian and uterine arteries the flaps remain well nourished, yet there is no troublesome hemorrhage from the beds from which they are raised. As with every other operation for prolapse, a thorough repair of the pelvic floor is essential.

Stricture of Female Urethra.—Although stricture of the female urethra is often looked upon as a rare condition, PUGH (*Ann. Surg.*, 1924, **79**, 770) found this condition in varying degree in 35 of 180 women presenting urological symptoms and therefore he calls the condition common. In this series the causative factor was gonorrhea in 24, chancroid 2, syphilis 1, childbirth trauma 1, keloid 1, possible focal infection 5. As this list shows, gonorrhea is probably the main factor in stricture of the urethra. In most cases frequency and dysuria are the symptoms most commonly complained of, and in several the symptoms more strongly suggested abdominal and renal lesions than they did urethral. Many cases present most remote symptoms, and if one is not careful, he may think the patients are neurotic. The retention of urine by women for long periods is so common that they often seem to think it a natural condition. Far more do women complain of dribbling (really an incontinence of retention) than they do of obstructive symptoms. Slight obstruction however, is often sufficient to produce a marked cystitis and urinary changes. Pugh states that we must no look for the classical text-book symptoms in urethral stricture in women, as it is unusual to find them. If, however, we take a careful history and find any suggestive urinary syptoms, we are justified in making a urethral examination. In fact, we should do it as a routine in all our female urological cases, using for the purpose either the olive tipped bougie or the bulb. The location of the stricture in this series was at the external meatus in 18, anterior third 12, middle third 1, posterior third 4. The prognosis depends largely on the etiological factor.

Soft infiltrations usually respond well to treatment, while the hard infiltrations are always a source of doubt as to their ultimate cure. In dilating these cases it is always best to begin the dilatation with the largest sound or bougie that will pass the stricture and then increase two numbers a week, until we reach the normal urethral caliber, which is about 26 F. After this, the large dilator should be passed once a month for a year, and even after that it will be wise to examine the patient every six months for evidence of return. In the hard infiltrations, the treatment must be more cautious than it is in the soft, as laceration of the urethra readily occurs. In cases of impassable stricture and even in some filiform strictures, it may be necessary to do a urethrotomy, which should be an internal urethrotomy if possible.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Effect of Loss of Sleep on the Composition of the Blood and Urine.—RAKESTRAW and WHITTIER (*Proc. Soc. Exper. Biol. and Med.* 1923, **21**, 5) conducted a series of experiments on 8 normal men, on a uniform diet, who remained awake over a period of forty-eight hours. Twenty-four-hour urine samples were collected for two days of the wakeful period, as well as the normal day preceding. Blood samples were taken at the beginning, middle and end of the period. The whole experiment was repeated after an interval of three weeks, the men alternating as controls and subjects in the two periods. Total nitrogen, urea, ammonia, chlorides, phosphates, uric acid and total acidity were determined in the urine by the customary methods; while in the blood, determinations were made of sugar, non-protein nitrogen, urea, phenols, uric acid, chlorides and alkali reserve. In 4 cases total "acid soluble" phosphorus and lactic acid were also determined in the blood. The results showed no really consistent alteration in any of the components studied with the exception of a possible increasing tendency of the total nitrogen and the phosphorus of the urine and an increase in the lactic acid and phosphorus of the blood. The data concerning these last two components were too fragmentary to justify any positive conclusion. No considerable alteration in the composition of human blood or urine was produced by the forty-eight-hour loss of sleep.

A Note on the Antigenic Properties of the Filtrate of Typhoid Saline Vaccine.—Inasmuch as PERLZWEIG and STEFFEN (*Jour. Exper. Med.*,

1923, **38**, 163) have shown that the immunizing antigen of the pneumococcus may be extracted from the bacterial cells by 70 per cent alcohol, physiological salt solution, and by water and that the supernatant fluid of old pneumococcus saline vaccines when filtered through a Berkefeld candle conferred active immunity upon mice after several subcutaneous injections, PERLZWEIG, WELLS and AMOSS (*Proc. Soc. Exper. Biol. and Med.*, 1923, **21**, 28) conducted a series of experiments on the antigenic properties of the supernatant fluids of other vaccines. Two rabbits were injected intravenously with successive doses of a triple typhoid saline vaccine and two with a Berkefeld (N) candle filtrate of the supernatant fluid of the same vaccine. The determinations of the agglutinin and precipitin titers of the rabbit sera indicated that it was possible to obtain in the sera of rabbits with the filtrate almost as high a titer as in the sera of rabbits treated with the whole vaccine. Their results showed that at least two of the antigens, the agglutinogen and precipitinogen, of the typhoid bacillus are soluble in and can be extracted by dilute salt solution. The authors state that "that these antigens are in all probability distinct from the higher protein constituents of the bacterial cell may be deduced by the heating of the vaccine in the process of manufacture and also by the fact that the supernatant filtrate used in this experiment gave a barely perceptible biuret reaction . . ."

Protection Against Typhoid-like Infections by Vaccinations. An Experimental Study.—"The basic fact that infections with the typhoid bacillus can be prevented by vaccination is, of course, well established by clinical evidence. It is also supported, theoretically, by a certain amount of experimental evidence. The experimental solution of these problems has been delayed by the impossibility of reproducing a true typhoid infection in the common laboratory animals. In the absence of a real protection test, efforts have been made to settle many questions by a quantitative determination of the antibody content of the serum of vaccinated animals. This method has been of practical value in some directions, but of course, in general, is inferior to an actual protection test." NICHOLS and STIMMEL (*Jour. Exper. Med.*, 1923, **38**, 283) took advantage of a spontaneous and severe epidemic among guinea-pigs, which furnished them with a picture of the natural disease, to ascertain the efficacy of a vaccine, using the causative organism, which was the "mutton" strain of B. *aertrycke*. Male guinea-pigs were inoculated, subcutaneously, at eight- to ten-day intervals and fifteen days after the last dose of vaccine were given the infecting dose of B. *aertrycke*, also subcutaneously. In each experiment, as far as possible, four animals were used, with four normal controls, and four controls vaccinated with fresh, full strength, saline vaccine, 1 cc of which contained about 1000 million organisms. Careful bacterial examinations of the blood, spleen, liver and gall-bladder were made on all animals that died. Under the conditions of the experiment, it was found that complete protection was secured by vaccination with full strength fresh saline vaccine, while 100 per cent of deaths occurred among the controls. The immunity acquired was variable and depended on the number of organisms injected. Vaccine kept ten to fourteen months gave less protection than vaccine eight months old and under.

Saline vaccine was more effective than lipovaccine, sensitized vaccine, or supernatant fluid vaccine. Resuspended vaccine was as effective as the original vaccine. In one experiment, group vaccine, made of typhoid Para A and Para B bacilli, was as effective as the original specific vaccine.

Serological Agglutination of Bacillus Sporogenes.—"The success of MEYER (*Jour. Infect. Dis.*, 1915, **17**, 458) in differentiating Vibrion septique, B. chauvoei and 'B. oedematis maligni' (B. sporogenes), and in identifying Vibrion septique by the agglutination test," led HALL and STARK (*Jour. Infect. Dis.*, 1923, **33**, 240) to use this method in differentiating and identifying certain pure cultures which had been unnamed. This procedure resulted in the segregation of 19 cultures which were later identified as B. sporogenes by their morphological and cultural characteristics. Marked differences in the titer of a given serum occurred when tested on different strains of this species, some strains of B. sporogenes failing to agglutinate even at 1 to 20. On the other hand, none of the sporogenes serums ever gave a positive test with any other species, nor did any serum prepared against another species ever agglutinate a strain of B. sporogenes. Consequently, the authors regarded "serological agglutination as a satisfactory criterion of species identity in properly controlled positive tests, but not of differentiation in negative tests." Immune serum was prepared by injecting a rabbit subcutaneously, with a forty-eight-hour glucose broth culture of B. sporogenes in 6 doses of 1 to 3 cc at intervals of two to three days during a period of two weeks. Following a rest of three weeks, 5 cc of blood were drawn from the ear and a slightly positive result was obtained at a dilution of 1 to 20. Subsequent injections increased the titer, the serum being active in a dilution of 1 to 1000. The agglutination tests were carried out at 37° C, using twenty-four or forty-eight-hour glucose broth cultures and readings were made after two hours' incubation. The authors conclude that agglutinating serums of high potency for B. sporogenes can be prepared easily by intravenous or subcutaneous injection of rabbits with glucose broth cultures; that these serums are specific for B. sporogenes and do not agglutinate other species; that there was a tendency toward strain specificity, more marked in some strains that others; that positive tests properly controlled identify, but negative tests may not differentiate some members of this species, except antigenically, and that sera from several other species of obligate anaërobes failed to agglutinate B. sporogenes.

The Study of Hemolytic Streptococci Associated with Scarlet Fever.—With the object of studying the agglutination of streptococci from the throats of patients with scarlet fever and the phenomenon of agglutinin absorption with these bacteria, STEVENS and DOCHEZ (*Proc. Soc. Exper. Biol. and Med.*, 1923, **21**, 39) collected strains from cases of scarlet fever occurring in several large cities of the United States and in Copenhagen, Denmark. From the throat cultures of 40 acute cases, hemolytic streptococci were isolated in 87.5 per cent, of which 74.3 per cent were agglutinated by immune sera prepared with two scarlatinal strains. Among the convalescents streptococci were found in 47.3 per cent and 55 per cent of these strains could be agglutinated with

scarlet immune sera. When strains obtained from a milk borne epidemic of scarlet fever and those obtained from scarlet fever occurring in the cities were examined for cross agglutination, it was found that, in the main, the cross agglutinations were consistent, and strains obtained from conditions other than scarlet fever were not agglutinated. In the absorption tests, which were performed at 55° C., fresh immune sera and strongly agglutinable strains were necessary for agglutinin absorption. All the combinations of sera and strains did not give absorption but each strain was represented in the absorption experiments, since absorption of agglutinin from several immune sera was accomplished with each strain or immune serum prepared with a given strain was absorbed by several other scarlet strains. The authors conclude that the strains of hemolytic streptococci associated with scarlet fever are closely related biologically, and probably constitute a single unit group.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Studies on the Relation of Mineral Dusts to Tuberculosis: III. The Relatively Early Lesions in Experimental Pneumokoniosis Produced by Carborundum Inhalation and Their Influence on Pulmonary Tuberculosis.—GARDNER (*Am. Rev. Tubere.*, 1923, **7**, 344) reports the results of his study of the effect of carborundum dust upon the normal and the tuberculous guinea-pig. He states that certain factors in the biological reaction of the normal and of the tuberculous animal to this irritant have been established. When this dust is inhaled it is widely distributed throughout the parenchyma of the lung. Once deposited, it tends to remain *in situ* but there is a tendency to focalization beneath the pleura and in the walls of relatively immobile structures like the sheaths of bloodvessels and bronchi. Although relatively small amounts are removed by way of the bronchi and by the lymphatic system to the tracheo-bronchial lymph nodes, it seems improbable, from the evidence at hand, that the lung would ever be able to rid itself of the major portion of the dust. Prolonged daily exposures finally cause an edematous condition in the bronchi and bronchioles which, however, rapidly subsides when the irritation is discontinued. The reaction of the normal lung to excessive quantities of this irritant is surprisingly insignificant. A true fibrosis in the parenchyma of the lung has never been observed. In the lymph nodes, on the other

hand, a definite fibrosis was frequently encountered. In the lung, in which carborundum inhalation is continued during the course of development of an inhalation tuberculosis, *extensive fibrosis is common.* The most remarkable result in this experiment has been the alteration in the course of the tuberculous process induced by the inhalation of this low virulent tubercle bacillus; from a self-limited process, which usually heals by resolution, it has been transformed into a progressive tuberculous bronchopneumonia. As a basis for this transformation it has been suggested that, through caseation of the primary focus, excessive amounts of dust have been liberated which attract new phagocytes to the area. By the agency of these phagocytes tubercle bacilli are accidentally transported to uninvolved portions of the lung and fresh foci of infection are established. Two other possible explanations have been suggested: (1) The mechanical obstruction to the drainage from the lung, as the result of fibrosis about the lymphatic vessels; (2) a direct effect of the dust upon the infecting organism. Opposed to the mechanical explanation is the observation that no fibrosis is present during the early stage of extension; later, when a generalized tuberculosis has developed, this factor may play some part. The argument that the bacillus may have been altered is met with the fact that there has been no serious extension to the abdominal viscera, such as regularly occurs when virulent bacilli are implanted in the lung tissue. In so far as proliferation of connective tissue may be considered as evidence of the ability of a mineral dust to injure pulmonary tissues, carborundum dust is apparently harmless to the normal lung, at least within the time limits of this experiment. If mere hardness and sharpness of a dust particle were sufficient to provoke fibroblastic proliferation characteristic of pneumokoniosis, carborundum dust should satisfy these conditions, for its hardness is between that of the ruby and the diamond, and its abrasive qualities are well known. The failure to produce this response in the lung may be considered negative evidence and favoring the chemical theory of the action of dust, which has been advanced by the English observers. As carborundum does not contain silicon in the crystalline form of silica, they would assume that it would not produce a silicosis. The mechanical hypothesis, suggested in explanation of the mechanism producing extension of partially healed tubercles, requires further investigation and will be controlled by the employment in a similar manner of other non-silicious dusts. However, it should always be borne in mind that silicosis in the human lung requires many years for its development and, while no hint of a proliferative process has been detected in the normal guinea-pig's lung, yet such a reaction might be produced if animals could be exposed for longer periods. The evidence for the solution of these problems is not to be found in such experiments as have been reported. These have been written more in the nature of preliminary communications than as finished results. They have served to determine the problems before us and to open up lines of investigation. Other work of a more fundamental character has been in progress for some time which, it is hoped, may illuminate the problem of the action of mineral dusts on pulmonary tissues.

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Studies on the Paratyphoid-enteritidis Group: III. An Epidemic of Food Infection Due to a Paratyphoid Bacillus of Rodent Origin.—SALTHE and KRUMWIEDE (*Am. Jour. Hyg.*, 1924, **4**, 23) report a food infection outbreak comprising fifty-nine cases. The cause of the outbreak was the contamination of the cream (cornstarch) filling of eclairs and crumb cake. The causative bacterium was a distinct paratyphoid type, Bacillus pestis caviæ (Bacillus typhi murium—"mutton type), prevalent in rodents; it has also been isolated from one other species. This type, only recently separated with definiteness as a distinct and prevalent paratyphoid variety, is apparently one of the commonest etiological agents of food infection in man. The Bacillus pestis caviæ, Bacillus cholera suis and Bacillus enteritidis are apparently the three varieties most likely to be expected in cases of food infection. One gains the impression that, had the Bacillus pestis caviæ type been recognized earlier as a distinct paratyphoid type, it might have been found to be the most common of the three varieties.

Some Observations on Anopheles.—BARBER and HAYNE (*U. S. Pub. Health Repts.*, 1924, **39**, 195), on the basis of observations made during the summer of 1920 and 1922 in a rice-growing region of Arkansas, state that anopheles in effective numbers spread about a mile from rice fields into an open country.

Some Observations on the Winter Activities of Anopheles in Southern United States.—BARBER, KOMP and HAYNE (*U. S. Pub. Health Repts.*, 1924, **39**, 231) studied the subject with special reference to determining whether winter, when the number of mosquitoes was reduced, furnished a season which might be profitably employed in antimosquito work. The results from this point of view were not encouraging. All stages of anopheles, ova, larvæ, pupæ and adults were found throughout the winter in southern Georgia, Alabama and Louisiana. There is no true hibernation, active adults of all species studied being found.

Some Notes on the Relation of Domestic Animals to Anopheles.—BARBER and HAYNE (*U. S. Pub. Health Repts.*, 1924, **39**, 139) sought to test the theory that domestic animals may serve, by furnishing a source of food for mosquitoes of the anopheles genus, to prevent the insects from biting man. They found that, given equal opportunities, mosquitoes fail to show preference for man, for the pig, or for the mule. It was also shown that feeding on pig's blood in no way impairs the taste of mosquitoes for human blood. The authors question, in general, the influence of animals in malaria prevalence.

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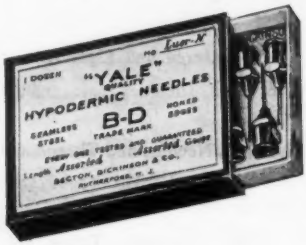

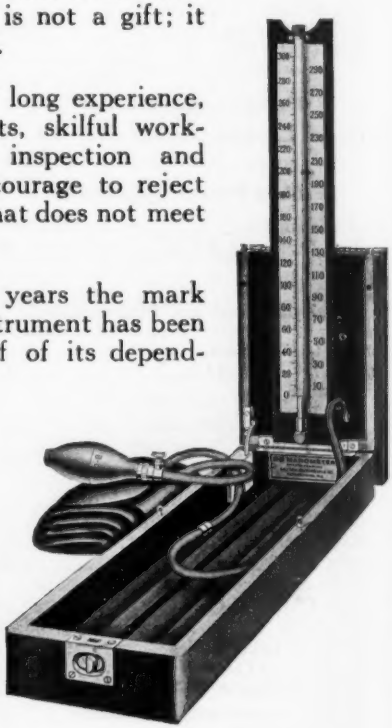

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